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Supplement 2: Methods and Results Supplement

Methods Supplement

NMA programming code

```
# Prerequisites: install and load package netmeta,
# if required, load packages required for netmeta are usually automatically loaded.
library(netmeta)

# data input:
# create a data frame nmadata containing
#       - study name (StName)
#       - treatment effect (te)
#       - standard error (se)
#       - name of first treatment (T1)
#       - name of second treatment/comparator (T2)
# values in brackets are variable names that appear in the following programming statements
# binary data: enter the logarithms of effects and standard error

# network meta-analysis for binary outcome, relative risk:
object.nma.results.bin <- netmeta(te ,se , T1, T2, StName, data=nmadata, sm="RR",
        comb.random=TRUE)

# results output:
exp(object.nma.results.bin$TE.random)       # treatment effect
exp(object.nma.results.bin$lower.random)   # 95% confidence interval lower bound
exp(object.nma.results.bin$upper.random)   # 95% confidence interval upper bound
```

```
# network meta-analysis for continuous outcome, mean difference:
object.nma.results.con  <- netmeta(te,se, T1, T2, StName, data=nmadata,sm="MD",
        comb.random=TRUE)

#Results output:
object.nma.results.con$TE.random          # treatment effect
object.nma. results.con$lower.random      # 95% confidence interval lower bound
object.nma. results.con$upper.random      # 95% confidence interval upper bound


# check for inconsistency:
netsplit(object.nma.results)              # for both binary and contiuous outcomes
```

Method for grading the certainty of conclusions

The certainty of the conclusions from an NMA is determined by the number of studies informing the pairwise contrasts, the inclusion of direct comparisons, the homogeneity of the studies and consistency of direct and indirect comparisons as well as the ROB of the studies contributing to an effect.

In general, results based on indirect comparisons or network meta-analyses are considered as having a low level of qualitative certainty of the results. Conclusions of moderate certainty can be reached by analyses in which the assumptions of similarity, homogeneity and consistency seem to be met well and if study-specific risks of bias are low. If indirect evidence is supported by direct evidence, then a high level of certainty may also be awarded.

Methods for sensitivity analyses

Two types of sensitivity analyses were conducted:

1) Sensitivity analyses to ensure assumptions of homogeneity and consistency are met

If any comparison within the network showed substantial heterogeneity and/or the network showed inconsistency, sensitivity analyses were performed to find possible clinical causes. All sensitivity analyses aimed at finding a study pool that did not conflict with the assumptions of homogeneity and consistency.

With a given study pool, the homogeneity assumption was checked for all contrasts with 2 or more studies. It was considered as substantial heterogeneity if the test of interaction in a random effects meta-analysis of the studies of a given contrast was significant at the 0.05 level. In such a case, sensitivity analyses were performed as described below and modified until a study pool free of substantial heterogeneity was available.

After homogeneity tests and, if applicable, sensitivity analyses, consistency tests were performed locally for all closed loops of the network. We chose the method of network splitting as proposed by [1]. Global tests exist too, but generally perform worse than local ones [2]. Inconsistency was assumed if a test was significant at the 0.05 level for a given loop. If inconsistency was found, sensitivity analyses were performed as shown below and modified until the study pool was regarded to be free of inconsistency:

Sensitivity analyses regarding homogeneity were performed for a given contrast. Sensitivity analyses regarding consistency were performed for the complete network at a given stage.

In the sensitivity analyses, the current study pool was analysed after removing all studies that showed deviations in terms of

- disease severity: studies with unknown or moderate severity were excluded
- biologics: studies with an unknown proportion or 5 – 20 % of patients pre-treated with biologics were excluded
- missing information on pre-treatment or disease severity: all studies lacking information were excluded
- disease severity: studies with very high disease severity were excluded
- study start: studies beginning before 2004 were excluded
- risk of bias: studies with a high risk of bias on the outcome level were excluded (only in the loop affected by inconsistency)

The order of the factors presented here is also the order in which the sensitivity analyses were performed. Sensitivity analyses were performed only if the original complete study pool or the pool after a previous sensitivity analysis still showed heterogeneity or inconsistency. If the NMA of a study pool for a given sensitivity analysis showed no substantial heterogeneity (in

any pairwise comparison) and no inconsistency, this study pool was considered as final. If the NMA of a study pool still showed substantial heterogeneity and/or inconsistency after the removal of studies, these studies were returned to the study pool and a sensitivity analysis regarding the next factor of the list as described above followed. If at the end of a series of sensitivity analyses a study pool still resulted that had substantial heterogeneity and/or inconsistency, all studies on an edge or in a loop affected were permanently removed from further analyses.

The study pool at the end of such a cascade of a sensitivity analysis fulfils the conditions of [3], i.e. that sufficient similarity, homogeneity and consistency can be assumed.

2) Sensitivity analyses to check the robustness of results with regard to minor deviations or uncertainties in similarity

If homogeneity and consistency can be assumed resulting from the procedure as given by 1), we as a matter of principle performed sensitivity analyses to check whether studies with

- unknown or deviant disease severity (S1)
- an unknown proportion or considerable amount of patients (5-20%) pretreated with biologics (S2)
- insufficient information on disease severity or pretreatment (S3)

had an influence on the results:

S1: performed only if at least 1 study included a population with unknown or deviant disease severity. Remove all studies from the starting pool with a population of unknown or deviant disease severity. Check again for homogeneity and inconsistency. If either is not fulfilled, perform the algorithm as given by 1). Compare results of S1 with those of the starting analysis with respect to the significance of the results. If any previously significant results have become insignificant or vice versa, maintain S1. Otherwise, put studies back into the study pool (i.e. the starting analysis is confirmed).

S2: Analysis on the basis of the results from the starting analysis (if confirmed by S1) or S1, now removing studies with an unknown proportion or considerable amount of patients (5-20%) pretreated with biologics. If any previously significant results have become insignificant or vice versa, maintain S2. Otherwise, put studies back into the study pool (i.e. the results after S1).

S3: Analysis on the basis of the results from S2, now removing studies with insufficient information on disease severity or pre-treatment. If any previously significant results have become insignificant or vice versa, maintain S3. Otherwise, put studies back into the study pool (i.e. the results after S2).

The study pool after S3 and its respective analysis form the final NMA.

Results Supplement

Study characteristics

Supplement Table 3: General characteristics of studies included in the systematic review

Study (year of initiation)	Blinding	Duration (relevant study part, weeks)	Interventions (N: No of patients in relevant study arms / n: No of patients considered, if applicable)	Combination with MTX, No of patients (%)	Pretreatment with MTX, No of patients (%)	Pretreatment with biologics, No of patients (%)	Concomitant medication allowed	Therapy adjustment [due to LOE], No of patients (%)	Study discontinued [due to LOE], No of patients (%)
AIM (2002)	double-blind	52	ABA + MTX (N = 435) PLC + MTX (N = 221)	433 (100) 219 (100)	432 (99.8) 219 (100)	9-10 (2.1-2.3) 5-6 (2.3-2.7)	low-dose oral corticosteroids (stable for 24 weeks), ≤ 2 corticosteroid injections / 24 weeks, NSAID	15 (3.5)* / 3 (0.7)† [NR] 26 (11.9)* / 5 (2.3)† [NR]	48 (11.1) [13 (3.0)] 57 (26.0) [40 (18.3)]
ASSURE (2002)	double-blind	52	ABA + / - DMARD (N = 959 / n = 859‡) PLC + / - DMARD (N = 482 / n = 423‡)	688 (80.4) 327 (78.2)	699 (81.7) 329 (78,7)	9-11 (1.1-1.3) 6-8 (1.4-1.9)	low-dose oral corticosteroids (stable for 12 weeks), NSAID	38 (4.4)* /48 (5.6)† [NR] 35 (8.4)* /18 (4.3)† [NR]	102 (11.9) [18 (2.1)] 67 (16.0) [30 (7.2)]
ATTEST (2005)	double-blind	24	ABA + MTX (N = 156) PLC + MTX (N = 110)	156 (100) 110 (100)	156 (100) 109 (99.1)	0 (0) 0 (0)	low-dose oral corticosteroids, NSAID	n/a	9 (5.8) [2 (1.3)] 3 (2.7) [1 (0.9)]
IM101071 (2006)	double-blind	24	ABA + MTX (N = 62 / n = 47§) PLC + MTX (N = 66 / n = 41§)	47 (100) 41 (100)	only pretreated patients included	pretreated patients excluded from re-analysis	low-dose oral corticosteroids, ≤ 2 corticosteroid injections, NSAID	n/a	0 (0) [0 (0)] 6 (14.6) [2 (4.9)]
IM101100 (2000)	double-blind	52	ABA + MTX (N = 115) PLC + MTX (N = 119)	113 (98.3) 117 (98.3)	113 (98.3) 118 (99.2)	2-3 (1.7-2.6) 2-3 (1.7-2.5)	low-dose oral corticosteroids, ≤ 2 corticosteroid injections, NSAID	2 (1.7) [NR] 3 (2.5) [NR]	25 (21.7) [13 (11,3)] 48 (40.3) [30 (25.2)]
IM101124 (2007)	double-blind	24	ABA + MTX (N = 55) PLC + MTX (N = 57)	55 (100) 57 (100)	55 (100) 57 (100)	3 (5.5) 0 (0)	low-dose oral corticosteroids, ≤ 2 corticosteroid injections, NSAID	0 (0)* / 1 (1.8)† [NR] 0 (0)* / 0 (0)† [NR]	2 (3.6) [0 (0)] 5 (8.8) [0 (0)]
ARMADA (1999)	double-blind	24	ADA + MTX (N = 67) PLC + MTX (N = 62)	67 (100) 62 (100)	67 (100) 62 (100)	TNFi pretreated patients excluded	low-dose oral corticosteroids, NSAID	n/a	18 (26.9) [17 (25.4)] 44 (71.0) [38 (61.3)]

Study (year of initiation)	Blinding	Duration (relevant study part, weeks)	Interventions (N: No of patients in relevant study arms / n: No of patients considered, if applicable)	Combination with MTX, No of patients (%)	Pretreatment with MTX, No of patients (%)	Pretreatment with biologics, No of patients (%)	Concomitant medication allowed	Therapy adjustment [due to LOE], No of patients (%)	Study discontinued [due to LOE], No of patients (%)
August II (2007)	not blinded for ADA	26	ADA + MTX (N = 79) PLC + MTX (N = 76)	79 (100) 76 (100)	79 (100) 76 (100)	pretreated patients excluded	low-dose oral corticosteroids, ≤ 1 corticosteroid injection, NSAID	n/a	4 (5.1) [NR] 7 (9.2) [NR]
DE019 (2000)	double-blind	52	ADA + MTX (N = 207) PLC + MTX (N = 200)	207 (100) 200 (100)	207 (100) 200 (100)	TNFi pretreated patients excluded	low-dose oral corticosteroids, ≤ 3 corticosteroid injections, NSAID	9 (4.3)* [NR] 33 (16.5)* [NR]	48 (23.2) [6 (2.9)] 60 (30.0) [23 (11.5)]
IM133001 (2011)	double-blind (unclear for ADA)	24	ADA + MTX (N = 59) MTX (N = 61)	planned for all patients	only pretreated patients included	pretreated patients excluded	low-dose oral corticosteroids (stable for 12 weeks), single corticosteroid injections as rescue treatment, NSAID	3 (5.1) [3 (5.1)] 8 (13.1) [8 (13.1)]	5 (8.5) [3 (5.1)] 14 (23.0) [12 (19.7)]
M02-556 (2003)	double-blind	24	ADA + MTX (N = 65) PLC + MTX (N = 63)	planned for all patients	65 (100) 63 (100)	TNFi pretreated patients excluded	low-dose oral corticosteroids, NSAID	8 (12.3) [8 (12.3)] 19 (30.2) [19 (30.2)]	6 (9.2) [0 (0)] 4 (6.3) [0 (0)]
ORAL STANDARD (2009)	double-blind	24	ADA + MTX (N = 204 / n = 185§) PLC + MTX (N = 108 / n = 96§)	planned for all patients	185 (100) 96 (100)	0 (0) 0 (0)	low-dose oral corticosteroids, ≤ 2 corticosteroid injections, NSAID	0 (0) [0 (0)] 42 (43.8) [42 (43.8)]	20 (10.8) [3 (1.6)] 13 (13.5) [5 (5.2)]
RADAR‖ (2010)	open	104	ADA + MTX (N = 40) Standard of care (N = 37)	39 (100) 35 (100)	39 (100) 35 (100)	0 (0) 0 (0)	oral corticosteroids, corticosteroid injections, NSAID, DMARDs	NR	12 (30.8) [2 (5.1)]¶ 6 (17.1) [2 (5.7)]¶
RA-BEAM (2012)	double-blind	24	ADA + MTX (N = 330) PLC + MTX (N = 489)	330 (100) 487 (100)	only pretreated patients included	pretreated patients excluded	low-dose oral corticosteroids, NSAID, HCQ or SSZ (stable dose)	40 (12.1) [40 (12.1)] 128 (26.2) [128 (26.2)]	24 (7.3) [3 (0.9)] 53 (10.9) [16 (3.3)]
STAR (2000)	double-blind	24	ADA + DMARD(s) (N = 318 / n = 178**) PLC + DMARD(s) (N = 318 / n = 199**)	178 (100) 199 (100)	176 (98.9) 195 (98.0)	TNFi pretreated patients excluded	low-dose oral corticosteroids, ≤ 3 corticosteroid injections up to week 12, NSAID	0 (0) [0 (0)] 3 (1.5) [3 (1.5)]*	12 (6.7) [1 (0.6)] 14 (7.0) [5 (2.5)]

Study (year of initiation)	Blin-ding	Dura-tion (rele-vant study part, weeks)	Interventions (N: No of patients in relevant study arms / n: No of patients considered, if applicable)	Combina tion with MTX, No of patients (%)	Pretreat-ment with MTX, No of patients (%)	Pretreatment with biologics, No of patients (%)	Concomitant medication allowed	Therapy adjustment [due to LOE], No of patients (%)	Study discontinued [due to LOE], No of patients (%)
990145 (1999)	double-blind	52	ANA + MTX (N = 453) PLC + MTX (N = 453)	449 (99.1) 450 (99.3)	only pretreated patients included	NR††	low-dose oral corticosteroids, ≤ 2 corticosteroid injections, NSAID	NR	139 (30.7) [NR] 153 (33.8) [NR]
990757 (1999)	double-blind	24	ANA + DMARD(s) (N = 1130 / n = 345**) PLC + DMARD(s) (N = 284 / n = 100**)	332 (96.2) 97 (97.0)	only pretreated patients included	NR††	oral corticosteroids (dose adjustments allowed), NSAID, DMARDs	n/a	81 (23) [2 (0.6)] 16 (16) [1 (1.0)]
20000198 (2001)	double-blind	24	ANA + MTX (N = 68) PLC + MTX (N = 68)	67 (98.5) 66 (97.1)	only pretreated patients included	TNFi pretreated patients excluded	low-dose oral corticosteroids, ≤ 2 corticosteroid injections	n/a	25 (37) [NR] 32 (47) [NR]
CERTAIN (2007)	double-blind	24	CZP + DMARD (N = 96) PLC + DMARD (N = 98)	81 (84.4) 79 (80.6)	pretreat-ment continued during study	1 (1.0) 0 (0)	low-dose oral corticosteroids, ≤ 1 corticosteroid injection up to week 8, NSAID, DMARDs	n/a	12 (12.5) [2 (2.1)] 18 (18.4) [7 (7.1)]
RA0025 (2009)	double-blind	24	CZP + MTX (N = 85 / n = 70§) PLC + MTX (N = 42 / n = 33§)	70 (100) 33 (100)	70 (100) 33 (100)	pretreated patients excluded from re-analysis	low-dose oral corticosteroids, ≤ 1 corticosteroid injection up to week 8, NSAID	n/a	20 (28.6) [16 (22.9)] 17 (51.5) [15 (45.5)]
RAPID 1 (2005)	double-blind	52	CZP + MTX (N = 393) PLC + MTX (N = 190)	392 (99.7) 198 (99.5)	392 (99.7) 198 (99.5)	11 (2.8) 7 (3.5)	low-dose oral corticosteroids, ≤ 3 corticosteroid injections (≤ 1 injection up to week 8), NSAID	n/a	138 (35.1) [98 (24.9)] 156 (78.4) [141 (70.9)]
RAPID 2 (2005)	double-blind	24	CZP + MTX (N = 246) PLC + MTX (N = 127)	246 (100) 127 (100)	246 (100) 127 (100)	9 (3.7) 6 (7.4)	low-dose oral corticosteroids, ≤ 1 corticosteroid injection up to week 8, NSAID	n/a	72 (29.3) [54 (22.0)] 110 (86.6) [107 (84.3)]

Study (year of initiation)	Blin-ding	Dura-tion (rele-vant study part, weeks)	Interventions (N: No of patients in relevant study arms / n: No of patients considered, if applicable)	Combina tion with MTX, No of patients (%)	Pretreat-ment with MTX, No of patients (%)	Pretreatment with biologics, No of patients (%)	Concomitant medication allowed	Therapy adjustment [due to LOE], No of patients (%)	Study discontinued [due to LOE], No of patients (%)
0881A1-4532‡‡ (2009)	open	24	ETA + MTX (N = 281) HCQ or SSZ + MTX (N = 142)‡‡	planned for all patients	NR	pretreated patients excluded	low-dose oral corticosteroids, ≤ 1 corticosteroid injection, NSAID	n/a	12 (4.3) [0 (0)] 13 (9.2) [1 (0.7)]
16.0014 (1997)	double-blind	24	ETA + MTX (N = 59) PLC + MTX (N = 30)	59 (100) 30 (100)	59 (100) 30 (100)	TNFi pretreated patients excluded	low-dose oral corticosteroids, NSAID	n/a	2 (3) [0 (0)] 6 (20) [4 (13)]
ENCOU-RAGE (2009)	open	52	ETA + MTX (N = 179) MTX (N = 43)	planned for all patients	only pretreated patients included	NR	low-dose corticosteroids	NR	18 (10.1) [NR] 29 (67.4) [16 (37.2)]§§
RACAT‡‡ (2007)	double-blind	48	ETA + MTX (N = 175) HCQ + SSZ + MTX (N = 178)‡‡	planned for all patients	pretreated patients included	NR	low-dose oral corticosteroids, ≤ 2 corticosteroid injections / 24 weeks, NSAID	44 (25.1) [44 (25.1)] 44 (24.7) [44 (24.7)]	19 (10.9) [-] 23 (12.9) [-]
TEMPO (2000)	double-blind	164	ETA + / - MTX (N = 231 / n = 101‖‖) PLC + / - MTX (N = 228 / n = 96‖‖)	101 (100) 96 (100)	101 (100) 96 (100)	TNFi pretreated patients excluded	low-dose oral corticosteroids (stable for 24 weeks), ≤ 2 corticosteroid injections from week 24-104, NSAID	n/a	18 (18) [4 (4)] 31 (32) [14 (14)]
C0524T28 (2010)	double-blind	24	GOL + MTX (N = 132) PLC + MTX (N = 132)	132 (100) 132 (100)	132 (100) 132 (100)	pretreated patients excluded	low-dose oral corticosteroids, ≤ 2 corticosteroid injections, NSAID	0 (0) [0 (0)] 65 (49.2) [65 (49.2)]	12 (9.1) [NR] 4 (3.0) [NR]
GO-FORTH (2008)	double-blind	24	GOL + MTX (N = 89) PLC + MTX (N = 90)	86 (96.6) 88 (97.8)	only pretreated patients included	pretreated patients excluded	low-dose oral corticosteroids, NSAID	NR [9 (10.1)] NR [28 (31.1)]	5 (5.6) [NR] 4 (4.4) [NR]
GO-FOR-WARD (2005)	double-blind	24	GOL + MTX (N = 89) PLC + MTX (N = 133)	88 (98.9) 133 (98.5)	only pretreated patients included	TNFi pretreated patients excluded	low-dose oral corticosteroids, ≤ 2 corticosteroid injections, NSAID	NR [15 (16.9)] NR [41 (30.8)]	1 (1) [NR] 7 (5.3) [NR]

Study (year of initiation)	Blinding	Duration (relevant study part, weeks)	Interventions (N: No of patients in relevant study arms / n: No of patients considered, if applicable)	Combination with MTX, No of patients (%)	Pretreatment with MTX, No of patients (%)	Pretreatment with biologics, No of patients (%)	Concomitant medication allowed	Therapy adjustment [due to LOE], No of patients (%)	Study discontinued [due to LOE], No of patients (%)
ATTRACT (1997)	double-blind	54	INF + MTX (N = 86) PLC + MTX (N = 88)	86 (100) 88 (100)	only pretreated patients included	NR¶¶	low-dose oral corticosteroids, cortico-steroid injections in single joints, NSAID	n/a	23 (26.7) [17 (19.8)] 44 (50.0) [32 (36.4)]
P04280 (2005)	double-blind	30	INF + MTX (N = 71) PLC + MTX (N = 72)	planned for all patients	only pretreated patients included	pretreated patients excluded	low-dose oral corticosteroids, ≤ 1 corticosteroid injection, NSAID	12 (16.9) [3 (4,2)] 9 (12.5) [3 (4.2)]	2 (2.8) [NR] 5 (6.9) [NR]
SWEFOT (2002)	open	86-90	INF + MTX (N = 128) SSZ + HCQ + MTX (N = 130)	planned for all patients	only pretreated patients included	pretreated patients excluded	oral corticosteroids, corticosteroid injections in single joints	10 (7.8) [NR] 6 (4.6) [NR]	38 (29.7) [5 (3.9)] 56 (43.1) [24 (18.5)]
CWP-TCZ301 (2009)	double-blind	24	TOC + DMARD(s) (N = 48 / n = 28**) PLC + DMARD(s) (N = 51 / n = 29**)	28 (100) 26 (100)	28 (100) 26 (100)	3 (6.3)*** 7 (13.7)***	low-dose oral corticosteroids, ≤ 1 corticosteroid injection, NSAID	0 (0) [0 (0)]*** 16 (31.4) [16 (31.4)]***	8 (16.7) [0 (0)]*** 11 (21.6) [5 (9.8)]***
LITHE (2004)	double-blind	52	TOC + MTX (N = 401 / n = 350§) PLC + MTX (N = 394 / n = 340§)	planned for all patients	only pretreated patients included	pretreated patients excluded from re-analysis (exception: HAQ-DI)	ow-dose oral corticosteroids, ≤ 1 corticosteroid injection / 24 weeks, NSAID	59 (15) [59 (15)]*** 195 (50) [195 (50)]***	57 (14,2) [2 (0,5)]*** 59 (15,1) [12 (3,0)]***
MEASURE (2007)	double-blind	24	TOC + MTX (N = 69 / n = 39§) PLC + MTX (N = 63 / n = 37§)	planned for all patients	only pretreated patients included	pretreated patients excluded from re-analysis	low-dose oral corticosteroids, ≤ 1 corticosteroid injection up to week 16, NSAID	NR [6 (15.4)] NR [12 (32.4)]	3 (7.7) [NR] 1 (2.7) [NR]
OPTION (2005)	double-blind	24	TOC + MTX (N = 205 / n = 193§) PLC + MTX (N = 204 / n = 184§)	planned for all patients	only pretreated patients included	pretreated patients excluded from re-analysis	low-dose oral corticosteroids, ≤ 1 corticosteroid injection, NSAID	NR [18 (9.3)] NR [61 (13.2)]	14 (7.3) [NR] 11 (6.0) [NR]
PORTRAIT‖ (2009)	double-blind	24	TOC + DMARD(s) (N = 35 / n = NR**‖) PLC + DMARD(s) (N = 19 / n = NR**‖)	32 (91.4) 16 (84.2)	NR	pretreated patients excluded	low-dose oral corticosteroids, NSAID	3 (8.6) [3 (8.6)] 10 (52.6) [10 (52.6)]	4 (11.4) [3 (8.6)] 2 (10.5) [0 (0)]

Study (year of initiation)	Blinding	Duration (relevant study part, weeks)	Interventions (N: No of patients in relevant study arms / n: No of patients considered, if applicable)	Combination with MTX, No of patients (%)	Pretreatment with MTX, No of patients (%)	Pretreatment with biologics, No of patients (%)	Concomitant medication allowed	Therapy adjustment [due to LOE], No of patients (%)	Study discontinued [due to LOE], No of patients (%)
ROSE (2007)	double-blind	24	TOC + DMARD(s) (N = 412 / n = 190§**) PLC + DMARD(s) (N = 207 / n = 81§**)	planned for all patients	only pretreated patients included	pretreated patients excluded from re-analysis	low-dose oral corticosteroids, ≤ 1 corticosteroid injection, NSAID	NR [25 (13.2)] NR [21 (25.9)]	23 (12.1) [NR] 13 (16.0) [NR]
TOWARD (2005)	double-blind	24	TOC + DMARD(s) (N = 805 / n = 353§**) PLC + DMARD(s) (N = 415 / n = 180§**)	planned for all patients	only pretreated patients included	pretreated patients excluded from re-analysis	low-dose oral corticosteroids, ≤ 1 corticosteroid injection up to week 16, NSAID	NR [10 (2.8)] NR [19 (10.6)]	25 (7.1) [NR] 11 (6.1) [NR]
TRACE (2008)	double-blind	24	TOC + DMARD(s) (N = 139 / n = 69§**) PLC + DMARD(s) (N = 70 / n = 40§**)	planned for all patients	only pretreated patients included	pretreated patients excluded from re-analysis	low-dose oral corticosteroids, ≤ 1 corticosteroid injection up to week 16, NSAID	NR [0 (0)] NR [3 (7.5)]	3 (4) [NR] 3 (8) [NR]
AMPLE (2009)	open	104	ABA + MTX (N = 318) ADA + MTX (N = 328)	318 (100) 326 (99.4)	318 (100) 325 (99.1)	pretreated patients excluded	low-dose oral corticosteroids, ≤ 2 corticosteroid injections or dose increases of oral corticosteroids / 52 weeks, NSAID, HCQ or SSZ	n/a	66 (20.8) [19 (6.0)] 83 (25.3) [16 (4.9)]
EXXELERATE (2011)	single-blind	102	CZP + MTX (N = 457) ADA + MTX (N = 458)	455 (99.6) 457 (99.8)	only pretreated patients included	2 (0.4) 2 (0.4)	low-dose oral corticosteroids, corticosteroid injections, NSAID	66 (14.4) [66 (14.4)]††† 59 (12.9) [59 (12.9)]†††	139 (30.4) [31 (6.8)]‡‡‡ 126 (27.5) [28 (6.1)]‡‡‡
RED SEA (2007)	open	52	ADA + DMARD(s) (N = 63 / n = 40**) ETA + DMARD(s) (N = 62 / n = 40**)	40 (100) 40 (100)	NR	TNFi pretreated patients excluded	unlimited use of corticosteroids, NSAID, DMARDs	NR	21 (33.3) [8 (12.7)]*** 26 (41.9) [8 (12.9)]***
WA25204 (2011)	open	≥ 260	TOC + DMARD(s) (N = 1538 / n = 1111**) ETA + DMARD(s) (N = 1542 / n = 1098**)	1111 (72.2)*** 1098 (71.2)***	1212 (78.8)*** 1205 (78.1)***	33 (2.1)*** 41 (2.7)***	unlimited use of corticosteroids, NSAID, DMARDs	401 (26.1) [37 (2.4)]*** 361 (23.4) [79 (5.1)]***	56 (3.6) [0 (0)]*** 67 (4.3) [0 (0)]***

Study (year of initiation)	Blin-ding	Dura-tion (rele-vant study part, weeks)	Interventions (N: No of patients in relevant study arms / n: No of patients considered, if applicable)	Combina tion with MTX, No of patients (%)	Pretreat-ment with MTX, No of patients (%)	Pretreatment with biologics, No of patients (%)	Concomitant medication allowed	Therapy adjustment [due to LOE], No of patients (%)	Study discontinued [due to LOE], No of patients (%)
Studies shown in dark grey were excluded from the analyses (reasons for exclusion are shown in dark grey); studies shown in light grey were excluded in the sensitivity analyses (reasons for exclusion are shown in light grey); * treatment with additional DMARDs; † discontinuation of DMARDs; ‡ treated in combination with DMARDs; § not pretreated with biologics; ‖ data for relevant part of study population not available; ¶ after 12 months; ** in combination with MTX without additional DMARDs; †† first TNFi was approved in the year of study initiation; ‡‡ no other study in the network had a matching comparator; §§ unclear if 16 or 30 patients adjusted therapy, numbers shown include 16 patients with adjustment; ‖‖ in combination with MTX; ¶¶ no TNFi approved in the year of study initiation; ***data shown refer to N (total No of patients in study arm); ††† therapy adjusted at week 12; ‡‡‡ discontinuation after 102 weeks ABA = abatacept; ADA = adalimumab; ANA = anakinra; CZP = certolizumab pegol; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; INF = infliximab; LOE = lack of efficacy; MTX = methotrexate; n/a = not applicable; No = number; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; PLC = placebo; SSZ = sulfasalazine; TNFi = tumour necrosis factor α inhibitor; TOC = tocilizumab								

Supplement Table 4: Patient and disease characteristics of studies included in the systematic review

Study (year of initiation)	Study arm	Age, years, mean (SD)	Gender, female / male (%)	Duration of disease, years, mean (SD)	Tender joint count / Swollen joint count (66 / 68 joint count), mean (SD)	DAS 28 (CRP) at baseline, mean (SD)	HAQ at baseline, mean (SD)	Erosion Score / TSS, mean (SD)
AIM (2002)	ABA + MTX	52 (13)	78 / 22	8.5 (7.3)	31.0 (13.2) / 21.4 (8.8)	6.4 (0.8)	1.7 (0.7)	22.0 (18.1) / 44.8 (37.3)
	PLC + MTX	50 (12)	82 / 18	8.9 (7.1)	32.3 (13.6) / 22.1 (8.8)	6.3 (0.8)	1.7 (0.6)	21.6 (18.5) / 44.3 (37.4)
ASSURE (2002)	ABA + / - DMARD	52 (12)	83 / 17	9.5 (8.7)	NR	NR	1.5 (0.6)	NR
	PLC + / - DMARD	52 (12)	83 / 17	9.5 (9.1)			1.5 (0.7)	
ATTEST (2005)	ABA + MTX	49 (13)	83 / 17	7.9 (8,5)	31.6 (13.9) / 21.3 (8.6)	6.4 (0.9)	1.8 (0.6)	NR
	PLC + MTX	49 (12)	87 / 13	8.4 (8,6)	30.3 (11.7) / 20.1 (7.0)	6.3 (0.8)	1.8 (0.7)	
IM101071 (2006)	ABA + MTX	53 (11)	83 / 17	7.1 (5.8)	20.5 (8.8) / 15.1 (5.6)	5.9 (0.7)	1.2 (0.6)	NR
	PLC + MTX	54 (12)	83 / 17	7.7 (7.1)	19.6 (7.3) / 16.8 (6.0)	5.8 (0.6)	1.4 (0.8)	
IM101100 (2000)	ABA + MTX	56 (13)	75 / 25	9.7 (9.8)	30.8 (12.2) / 21.3 (8.4)	6.2 (0.7)	1.0 (0.5)*	21.8 (17.8) / 51.0 (43.2)
	PLC + MTX	55 (12)	66 / 34	8.9 (8.3)	29.2 (13.0) / 21.8 (8.8)	6.2 (0.9)	1.0 (0.6)*	18.5 (16.2) / 44.2 (39.6)
IM101124 (2007)	ABA + MTX	47 (12)	86 / 14	9.4 (6.3)	25.3 (13.0) / 15.2 (5.5)	5.9 (0.9)	1.6 (0.7)	NR
	PLC + MTX	50 (11)	86 / 14	9.7 (6.8)	25.3 (15.7) / 13.9 (4.4)	5.7 (0.7)	1.5 (0.6)	
ARMADA (1999)	ADA + MTX	57 (11)	75 / 25	12.2 (11.1)	28.0 (12.7) /17.3 (8.6)	5.6 (0.8)	1.6 (0.6)	NR
	PLC + MTX	56 (11)	82 / 18	11.1 (8.0)	28.7 (15.2) / 16.9 (9.5)	5.7 (1.1)	1.6 (0.6)	
August II (2007)	ADA + MTX	53 (12)	81 / 19	8.8 (7.4)	27.6 (14.0) / 15.9 (7.7)	5.8 (1.0)	1.6 (0.5)	NR
	PLC + MTX	54 (10)	84 / 16	8.4 (7.4)	26.1 (11.3) / 17.1 (8.3)	5.8 (1.0)	1.7 (0.6)	
DE019 (2000)	ADA + MTX	56 (14)	76 / 24	11.0 (9.2)	27.3 (12.7) / 19.3 (9.8)	5.6 (0.9)	1.5 (0.6)	41.4 (33.4) / 72.1 (60.7)
	PLC + MTX	56 (12)	73 / 27	10.9 (8.8)	28.1 (13.8) / 19.0 (9.5)	5.8 (0.9)	1.5 (0.6)	37.2 (25.8) / 66.4 (47.4)
IM133001 (2011)	ADA + MTX	53 (11)	81 / 19	6.1 (7.5)	30.0 (16.1) / 18.0 (11.1)	6.3 (1.1)	1.9 (0.6)	NR
	MTX	51 (11)	75 / 25	6.4 (8.1)	28.5 (15.7) / 18.3 (11.0)	6.1 (0.9)	1.6 (0.6)	
M02-556 (2003)	ADA + MTX	49 (10)	95 / 5	6.8 (4.2)†	19.2 (9.2) / 12.2 (5.6)	5.4 (0.9)	1.4 (0.6)	NR
	PLC + MTX	50 (11)	86 / 14	6.9 (4.5)†	20.3 (8.6) / 12.8 (5.8)	5.6 (0.9)	1.3 (0.6)	
ORAL STANDARD (2009)	ADA + MTX	53 (12)	79 / 21	7.9 (7.5)	26.5 (15.3) / 16.1 (8.3)	5.6 (1.0)	1.5 (0.6)	NR
	PLC + MTX	54 (14)	77 / 23	7.5 (8.0)	26.9 (14.4) / 16.8 (9.1)	5.6 (0.9)	1.4 (0.7)	

Study (year of initiation)	Study arm	Age, years, mean (SD)	Gender, female / male (%)	Duration of disease, years, mean (SD)	Tender joint count / Swollen joint count (66 / 68 joint count), mean (SD)	DAS 28 (CRP) at baseline, mean (SD)	HAQ at baseline, mean (SD)	Erosion Score / TSS, mean (SD)
RADAR (2010)	ADA + MTX	52 (12)	67 / 33	0.7 (0.5)	21.4 (13.8) / 13.4 (6.4)	5.4 (1.0)	1.4 (0.8)	6.4 (12.3) / 10.7 (20.1)
	Standard of care	54 (10)	69 / 31	0.8 (0.4)	20.9 (11.4) / 13.8 (7.9)	5.4 (1.0)	1.4 (0.6)	5.3 (9.0) / 8.4 (14.1)
RA-BEAM (2012)	ADA + MTX	53 (12)	76 / 24	8,3 (7,9)	23.4 (13.7) / 15.4 (9.1)	5.8 (0.9)	1,6 (0,7)	26.4 (28.7) / 44.4 (50.9)
	PLC + MTX	53 (12)	78 / 22	8,9 (8,0)	23.3 (13.5) / 15.5 (9.4)	5.7 (1.0)	1,6 (0,7)	26.8 (28.6) / 45.1 (50.2)
STAR (2000)	ADA + DMARD(s)	55 (12)	79 / 21	8,9 (8,7)	27.5 (12.6) / 21.2 (11.5)	5.6 (0.9)	1,3 (0,6)	NR
	PLC + DMARD(s)	55 (12)	83 / 17	11,1 (9,3)	26.3 (12.8) / 20.9 (10.5)	5.5 (0.8)	1,4 (0,6)	
990145 (1999)	ANA + MTX	56 (12)	80 / 20	10.7 (9.1)	27.0 (15.0) / 20.8 (11.6)	5.8 (0.9)	1.4 (0.6)	24.9 (20.4) / 49.5 (39.1)
	PLC + MTX	56 (12)	75 / 25	9.9 (8.3)	25.6 (13.9) / 20.1 (10.5)	5.7 (0.9)	1.4 (0.6)	28.0 (23.5) / 52.2 (43.4)
990757 (1999)	ANA + DMARD(s)	56 (12)	75 / 25	10.1 (9.9)	21.8 (14.4) / 17.9 (11.4)	5.4 (1.1)	1.4 (0.7)	NR
	PLC + DMARD(s)	56 (13)	78 / 22	9.2 (8.4)	22.6 (13.3) / 17.0 (9.7)	5.4 (1.1)	1.4 (0.6)	
20000198 (2001)	ANA + MTX	55 (11)	81 / 19	10.8 (10.6)	30.4 (14.1) / 20.7 (10.0)	6.2 (0.8)	1.7 (0.6)	NR
	PLC + MTX	54 (12)	88 / 12	8.3 (7.2)	29.4 (14.4) / 21.1 (11.3)	6.0 (1.0)	1.5 (0.6)	
CERTAIN (2007)	CZP + DMARD	54 (12)	84 / 16	4.5 (3.5)	3.7 (1.5) / 3.4 (1.5)‡	4.5 (0.4)§	1.1 (0.6)	NR
	PLC + DMARD	54 (12)	77 / 23	4.7 (3.3)	3.9 (1.6) / 3.2 (1.3)‡	4.5 (0.3)§	1.0 (0.6)	
RA0025 (2009)	CZP + MTX	52 (12)	89 / 11	5.9 (4.1)	12.2 (6.4) / 9.2 (4.7)	6.3 (0.9)§	1.4 (0.7)	NR
	PLC + MTX	51 (11)	91 / 9	4.9 (4.3)	14.5 (6.5) / 11.3 (5.5)	6.6 (1.0)§	1.6 (0.8)	
RAPID 1 (2005)	CZP + MTX	51 (12)	82 / 18	6.1 (4.2)	30.8 (12.4) / 21.7 (9.9)	6.9 (0.8)§	1.7 (0.6)	14.9 (24.3) / 38.4 (49.4)
	PLC + MTX	52 (11)	84 / 16	6.2 (4.4)	29.8 (13.0) / 21.2 (9.7)	7.0 (0.9)§	1.7 (0.6)	14.3 (20.7) / 39.0 (44.5)
RAPID 2 (2005)	CZP + MTX	52 (11)	84 / 16	6.1 (4.1)	30.1 (14.5) / 20.5 (9.6)	6.9 (0.8)§	1.6 (0.6)	19.0 (26.8) / 39.6 (50.1)
	PLC + MTX	52 (12)	84 / 16	5.6 (3.9)	30.4 (13.4) / 21.9 (9.7)	6.8 (0.9)§	1.6 (0.6)	23.1 (32.1) / 46.5 (58.6)
0881A1-4532 (2009)	ETA + MTX	48 (12)	88 / 12	7.9 (7.0)	25.1 (11.9) / 18.2 (8.4)‖	6.6 (0.7)§	1.6 (0.7)	NR
	HCQ or SSZ + MTX	49 (11)	90 / 10	9.0 (7.5)	26.2 (12.3) / 19.3 (10.1)‖	6.7 (0.8)§	1.6 (0.7)	
16.0014 (1997)	ETA + MTX	48 (11)	90 / 10	13.3 (9.1)	27.9 (14.5) / 21.3 (10.6)¶	4.6 (0.9)	1.5 (0.6)	NR
	PLC + MTX	53 (10)	73 / 27	12.7 (9.4)	27.5 (15.1) / 20.3 (11.2)¶	4.5 (0.9)	1.3 (0.8)	

Study (year of initiation)	Study arm	Age, years, mean (SD)	Gender, female / male (%)	Duration of disease, years, mean (SD)	Tender joint count / Swollen joint count (66 / 68 joint count), mean (SD)	DAS 28 (CRP) at baseline, mean (SD)	HAQ at baseline, mean (SD)	Erosion Score / TSS, mean (SD)
ENCOU-RAGE (2009)	ETA + MTX	53 (14)**	86 / 14**	2.0 (1.4)**	3.2 (1.9) / 4.0 (3.7)‖**	3.5 (0.7)**	0.8 (0.6)**	7.2 (11.8) / 15.0 (20.4)**
	MTX	53 (14)**	83 / 17**	1.9 (1.3)**	3.0 (1.9) / 3.4 (2.5)‖**	3.4 (0.7)**	0.8 (0.5)**	7.2 (12.2) / 15.8 (22.6)**
RACAT (2007)	ETA + MTX	56 (13)	49 / 51	4.9 (8.0)	13.3 (6.4) / 11.3 (5.2)‡	5.9 (0.9)††	1.5 (0.8)	NR / 16.3 (22.0)
	HCQ + SSZ + MTX	58 (13)	43 / 57	5.5 (9.3)	13.4 (6.6) / 11.1 (5.3)‡	5.8 (0.9)††	1.4 (0.8)	NR / 20.4 (29.2)
TEMPO (2000)	ETA + / - MTX	53 (11)	72 / 28	8.8 (5.1)	36.3 (14.1) / 24.0 (11.5)¶	6.5 (0.9)	1.8 (0.6)	30.2 (33.1) / 51.4 (56.5)
	PLC + / - MTX	54 (11)	80 / 20	9.5 (5.2)	36.8 (13.4) / 24.3 (11.5)¶	6.5 (0.8)	1.9 (0.7)	33.1 (38.4) / 49.5 (61.3)‡‡
C0524T28 (2010)	GOL + MTX	48 (11)	83 / 17	7.6 (7.1)	22.9 (15.4) / 10.7 (7.0)	5.4 (1.1)	1.3 (0.7)	NR
	PLC + MTX	47 (12)	79 / 21	8.0 (7.3)	22.5 (14.8) / 11.8 (7.4)	5.5 (1.1)	1.2 (0.8)	
GO-FORTH (2008)	GOL + MTX	50 (10)	85 / 15	8.8 (8.8)	13.1 (8.4) / 11.8 (6.7)	4.9 (1.0)	1.0 (0.6)	32.1 (34.7) / 58.0 (62.4)
	PLC + MTX	51 (12)	83 /17	8.7 (8.2)	13.2 (7.8) / 11.4 (6.6)	5.0 (0.9)	1.0 (0.7)	30.8 (37.1) / 54.2 (62.9)
GO-FORWARD (2005)	GOL + MTX	50 (11)	81 / 19	7.3 (7.8)	27.9 (15.8) / 16.8 (11.8)	5.6 (1.1)	1.4 (0.7)	NR
	PLC + MTX	51 (12)	82 / 18	8.6 (7.9)	24.9 (14.7) / 14.8 (9.4)	5.4 (1.0)	1.3 (0.7)	
ATTRACT (1997)	INF + MTX	54 (11)	81 / 19	9.8 (8.2)	32 (18) / 22 (12)	6.3 (1.1)	1.8 (0.6)	NR / 78.8 (73.4)
	PLC + MTX	51 (12)	80 / 20	10.7 (8.3)	31 (18) / 21 (12)	6.1 (1.1)	1.7 (0.6)	NR / 81.9 (77.3)
P04280 (2005)	INF + MTX	49 (10)	90 / 10	8.1 (6.5)	25.2 (17.3) / 20.3 (14.0)‖	NR	1.4 (0.7)	NR
	PLC + MTX	51 (11)	89 / 11	10.9 (8.7)	23.9 (15.7) / 19.0 (11.6)‖		1.4 (0.7)	
SWEFOT (2002)	INF + MTX	51 (13)	76 / 24	0.5 (0.3)	NR	4.9 (1.0)††	1.3 (0.6)	1.8 (3.6) / 4.6 (7.3)
	SSZ + HCQ + MTX	53 (14)	78 / 22	0.5 (0.3)		4.8 (1.1)††	1.3 (0.6)	2.4 (5.5) / 5.5 (9.4)
CWP-TCZ301 (2009)	TOC + DMARD(s)	53 (10)§§	89 / 11§§	10.8 (7.8)§§	21.8 (12.1) / 10.3 (4.9)‡§§	6.1 (0.8)††§§	1.3 (0.7)§§	NR
	PLC + DMARD(s)	52 (12)§§	88 / 12§§	8.9 (7.2)§§	22.8 (14.0) / 11.9 (10.0)‡§§	6.1 (1.1)††§§	1.4 (0.6)§§	
LITHE (2004)	TOC + MTX	53 (12)	82 / 18	8.9 (8.2)	29.3 (15.3) / 17.2 (9.3)	6.5 (1.0)§	1.5 (0.6)	NR / 24.4 (25.7)
	PLC + MTX	51 (12)	83 / 17	8.5 (8.0)	28.0 (14.8) / 16.5 (9.2)	6.5 (0.9)§	1.5 (0.6)	NR / 24.5 (26.7)
MEASURE (2007)	TOC + MTX	55 (10)	79 / 21	7.0 (8.9)	33.5 (17.5) / 16.3 (9.9)	6.6 (0.9)§	1.6 (0.6)	NR
	PLC + MTX	55 (10)	65 / 35	6.0 (6.0)	29.5 (17.6) / 17.0 (12.0)	6.4 (1.0)§	1.5 (0.6)	

Study (year of initiation)	Study arm	Age, years, mean (SD)	Gender, female / male (%)	Duration of disease, years, mean (SD)	Tender joint count / Swollen joint count (66 / 68 joint count), mean (SD)	DAS 28 (CRP) at baseline, mean (SD)	HAQ at baseline, mean (SD)	Erosion Score / TSS, mean (SD)
OPTION (2005)	TOC + MTX	51 (12)	84 / 16	7.5 (7.4)	31.8 (15.2) / 19.6 (11.5)	6.8 (0.9)§	1.5 (0.6)‖‖	NR
	PLC + MTX	50 (12)	77 / 23	7.3 (7.1)	32.7 (15.7) / 20.8 (11.8)	6.8 (0.9)§	1.5 (0.6)‖‖	
PORTRAIT (2009)	TOC + DMARD(s)	54 (51)§§¶¶	83 / 17§§	6.0§§¶¶	11.0 (28) / 8.5 (21)‡§§¶¶	5.3 (1.0)§§¶¶	2.1 (1.6)§§¶¶	NR
	PLC + DMARD(s)	54 (24)§§¶¶	90 / 10§§	5.0§§¶¶	13.0 (25) / 10.0 (24)‡§§¶¶	5.3 (1.1)§§¶¶	2.3 (1.5)§§¶¶	
ROSE (2007)	TOC + DMARD(s)	56 (12)	80 / 20	7.3 (8.1)	29.2 (16.0) / 19.8 (11.9)	6.4 (1.1)§	5.2 (1.8)***	NR
	PLC + DMARD(s)	55 (12)	86 / 14	7.0 (9.1)	30.4 (16.2) / 19.0 (10.5)	6.5 (0.9)§	5.1 (2.0)***	
TOWARD (2005)	TOC + DMARD(s)	54 (12)	82 / 18	9.7 (8.9)	30.1 (16.4) / 19.5 (11.8)	6.7 (0.9)§	1.5 (0.6)	NR
	PLC + DMARD(s)	54 (13)	82 / 18	9.6 (9.5)	29.1 (14.7) / 18.8 (10.7)	6.6 (1.0)§	1.5 (0.6)	
TRACE (2008)	TOC + DMARD(s)	47 (10)	87 / 13	4.3 (4.8)	27.3 (14.4) / 16.1 (9.2)	6.7 (0.9)§	1.4 (0.6)	NR
	PLC + DMARD(s)	48 (12)	80 / 20	4.2 (4.8)	21.7 (13.5) / 14.2 (10.1)	6.5 (0.7)§	1.3 (0.5)	
AMPLE (2009)	ABA + MTX	51 (13)	81 / 19	1.9 (1.4)	25.4 (15.3) / 15.8 (9.8)‡	5.5 (1.1)	1.5 (0.7)	10.5 (17.9) / 19.2 (32.3)
	ADA + MTX	51 (13)	82 / 18	1.8 (1.4)	26.3 (15.8) / 15.9 (10.0)‡	5.5 (1.1)	1.5 (0.7)	10.6 (15.6) / 19.2 (28.6)
EXXELE-RATE (2011)	CZP + MTX	54 (12)	79 / 21	6.0 (6.9)	14.8 (6.5) / 10.9 (4.9)‡	5.6 (0.9)	1.5 (0.6)	NR
	ADA + MTX	53 (13)	79 / 21	5.8 (6.9)	15.2 (6.5) / 11.2 (5.1)‡	5.7 (0.9)	1.5 (0.6)	
RED SEA (2007)	ADA + DMARD(s)	55 (13)§§	75 / 25§§	7.0 (3; 13)§§¶¶	14 (9; 20) / 9 (5; 12)§§‡¶¶	5.6 (0.9)§§	NR	NR
	ETA + DMARD(s)	53 (13)§§	70 / 30§§	5.5 (2; 15)§§¶¶	14 (8; 20) / 9 (6; 13)§§‡¶¶	5.8 (0.9)§§		
WA25204 (2011)	TOC + DMARD(s)	61 (7)§§	78 / 22§§	10.2 (9.0)§§	NR	NR	NR	NR
	ETA + DMARD(s)	61 (8)§§	78 / 22§§	10.1 (9.3)§§				

Studies shown in dark grey were excluded from the analyses (reasons for exclusion are shown in dark grey); studies shown in light grey were excluded in the sensitivity analyses (reasons for exclusion are shown in light grey)

* modified HAQ; † data refer to different No of patients (ADA: 37, PLC: 36); ‡ 28 joint count; § ESR included instead of CRP; ‖ unclear which type of joint count; ¶ 71 / 68 joint count; ** data refer to different number of patients (ETA: 161, PLC: 30); †† unclear if CRP or ESR included; data refer to different number of patients (PLC: 81); §§ data shown refer to N (total No of patients in study arm); ‖‖ data refer to different number of patients (TOC: 161, PLC: 151); ¶¶ median (Q1; Q3) or median (range); *** MDHAQ

ABA = abatacept; ADA = adalimumab; ANA = anakinra; CRP = C-reactive protein; CZP = certolizumab pegol; DAS 28 = disease activity score based on 28 joints; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; ETA = etanercept; GOL = golimumab; HAQ = health assessment questionnaire; INF = infliximab; MDHAQ = multidimensional health assessment questionnaire; MTX = methotrexate; No = number; NR = not reported; PLC = placebo; Q = quartile; SD = Standard Deviation; TOC = tocilizumab; TSS = total sharp score

Risk of bias assessments

Supplement Table 5: Risk of bias assessment on the study level

Study	Random sequence generation adequate	Allocation concealment	Blinding of participants	Blinding of personnel	Selective reporting unlikely	No other aspects generating bias	Risk of bias on study level
Adalimumab + MTX vs. Placebo + MTX							
ARMADA	unknown*	yes	yes	yes	yes	yes	low
August II	yes	yes	no†	no†	yes	yes	high
DE019	unknown*	yes	yes	yes	yes	yes	low
IM133001	unknown*	unknown*	unknown*	yes	yes	yes	high
M02-556	unknown*	yes	yes	yes	yes	yes	low
ORAL STANDARD	unknown*	yes	yes	yes	yes	yes	low
RA-BEAM	yes	yes	yes	yes	yes	yes	low
STAR	unknown*	yes	yes	yes	yes	yes	low
Certolizumab pegol + MTX vs. Placebo + MTX							
CERTAIN	unknown*	yes	yes	yes	yes	yes	low
RAPID 1	unknown*	yes	yes	yes	yes	yes	low
RAPID 2	unknown*	yes	yes	yes	yes	yes	low
RA0025	unknown*	yes	yes	yes	yes	yes	low
Anakinra + MTX vs. Placebo + MTX							
990145	unknown*	yes	yes	yes	yes	yes	low
990757	yes	yes	yes	yes	yes	yes	low
20000198	unknown*	unknown*	yes	yes	yes	yes	high
Etanercept + MTX vs. Placebo + MTX							
16.0014	yes	yes	yes	yes	yes	yes	low
Infliximab + MTX vs. Placebo + MTX							
ATTRACT	unknown*	yes	yes	yes	yes	yes	low
Tocilizumab + MTX vs. Placebo + MTX							
LITHE	unknown*	yes	yes	yes	yes	yes	low
MEASURE	unknown*	yes	yes	yes	yes	yes	low
OPTION	unknown*	yes	yes	yes	yes	yes	low
ROSE	unknown*	yes	yes	yes	yes	yes	low
TOWARD	unknown*	yes	yes	yes	yes	yes	low
TRACE	unknown*	yes	yes	yes	yes	yes	low
Abatacept + MTX vs. Adalimumab + MTX							
AMPLE	yes	yes	no	yes	yes	yes	low
Adalimumab + MTX vs. Certolizumab pegol + MTX							
EXXELERATE	yes	yes	no	yes	yes	yes	low
* Information for assessment not available; † no blinding for the adalimumab + MTX treatment group MTX = methotrexate							

Supplement Table 6: Risk of bias assessment for remission (CDAI ≤ 2.8)

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	no	yes	yes	yes	high
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	no	unknown*	yes	yes	high
* Insufficient information for assessment CDAI = clinical disease activity index; ITT = intention-to treat; MTX = methotrexate						

Supplement Table 7: Risk of bias assessment for low disease activity (CDAI ≤ 10)

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Adalimumab + MTX vs. Placebo + MTX						
ARMADA	low	yes	yes	yes	yes	low
August II	high	no*	yes	yes	yes	high
DE019	low	yes	no†	yes	yes	high
M02-556	low	yes	yes	yes	yes	low
ORAL STANDARD	low	yes	yes	yes	yes	low
RA-BEAM	low	yes	yes	yes	yes	low
STAR	low	yes	yes	yes	yes	low
Certolizumab pegol + MTX vs. Placebo + MTX						
RAPID 1	low	yes	unknown‡	yes	yes	high
RAPID 2	low	yes	unknown‡	yes	yes	high
RA0025	low	yes	yes	yes	yes	low
Infliximab + MTX vs. Placebo + MTX						
ATTRACT	low	yes	yes	yes	yes	low
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	no	unknown‡	yes	yes	high
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	no	unknown‡	yes	yes	high
* No blinding for the adalimumab + MTX treatment group; † large differences in the proportion of patients who prematurely discontinued the study between the treatment groups; ‡ insufficient information for assessment; CDAI = clinical disease activity index; ITT = intention-to treat; MTX = methotrexate						

Supplement Table 8: Risk of bias assessment for serious adverse events and infections

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	yes	yes	yes	yes	low
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	yes	yes	yes	yes	low
ITT = intention-to treat; MTX = methotrexate						

Supplement Table 9: Risk of bias assessment for pain (VAS)

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Adalimumab + MTX vs. Placebo + MTX						
ARMADA	low	yes	no*	no†	yes	high
August II	high	no‡	no§	no§	yes	high
DE019	low	yes	no*	yes	yes	high
IM133001	high	unknown‖	unknown*	yes	yes	high
M02-556	low	yes	no¶	yes	yes	high
ORAL STANDARD	low	yes	unknown**	yes	yes	high
RA-BEAM	low	yes	no*	yes	yes	high
STAR	low	yes	yes	yes	yes	low
Certolizumab pegol + MTX vs. Placebo + MTX						
CERTAIN	low	yes	no††	yes	yes	high
RAPID 1	low	yes	unknown*	yes	yes	high
RAPID 2	low	yes	unknown*	yes	yes	high
RA0025	low	yes	no*	yes	yes	high
Etanercept + MTX vs. Placebo + MTX						
16.0014	low	yes	no*	yes	yes	high
Infliximab + MTX vs. Placebo + MTX						
ATTRACT	low	yes	no‡‡	yes	yes	high
Tocilizumab + MTX vs. Placebo + MTX						
LITHE	low	yes	no‡‡	yes	yes	high
MEASURE	low	yes	no‡‡	yes	yes	high
OPTION	low	yes	no‡‡	yes	yes	high
TOWARD	low	yes	no‡‡	yes	yes	high
TRACE	low	yes	yes	yes	yes	low
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	no	unknown‖	yes	yes	high
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	no	unknown‖	yes	yes	high

* Large differences in the proportion of patients who prematurely discontinued the study and / or the study treatment between the treatment groups; † ANCOVA analysis not conducted as planned; ‡ no blinding for the adalimumab + MTX treatment group; § analysis not conducted as planned regarding the handling of missing data (high proportion of patients potentially not considered); ‖ insufficient information for assessment; ¶ high proportion of patients with missing data imputed with LOCF and large differences in the proportion of these patients between the treatment groups; ** high proportion of patients with therapy adjustment in the comparator group; †† proportion of missing data unknown; ‡‡ high proportion of patients not considered in the analysis and large differences in the proportion of these patients between the treatment groups

ANCOVA = analysis of covariance; ITT = intention-to treat; LOCF: last observation carried forward; MTX = methotrexate; VAS = visual analogue scale

Supplement Table 10: Risk of bias assessment for physical function (HAQ-DI)

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Infliximab + MTX vs. Placebo + MTX						
ATTRACT	low	yes	unknown*	yes	yes	high
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	no	unknown†	yes	yes	high
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	no	unknown†	yes	yes	high
* Potentially large differences in the proportion of patients not considered in the analysis; † insufficient information for assessment HAQ-DI = health assessment questionnaire – disability index; ITT = intention-to treat; MTX = methotrexate						

Supplement Table 11: Risk of bias assessment for health related quality of life (SF-36)

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Anakinra + MTX vs. Placebo + MTX						
990145	low	yes	yes	yes	yes	low
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	no	unknown*	yes	yes	high
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	no	unknown*	yes	yes	high
* Insufficient information for assessment ITT = intention-to treat; MTX = methotrexate; SF-36 = short form 36 health survey						

Supplement Table 12: Risk of bias assessment for fatigue (VAS / NRS / BRAF-MDQ)

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	no	unknown*	yes	yes	high
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	no	unknown*	yes	yes	high
* Insufficient information for assessment BRAF-MDQ = Bristol rheumatoid arthritis fatigue - multidimensional questionnaire; ITT = intention-to treat; MTX = methotrexate; NRS = numerical rating scale; VAS = visual analogue scale						

Supplement Table 13: Risk of bias assessment for discontinuation due to adverse event

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Anakinra + MTX vs. Placebo + MTX						
990145	low	yes	unknown*	yes	yes	high
990757	low	yes	yes	yes	yes	low
20000198	high	yes	unknown*	yes	yes	high
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	unknown†	yes	yes	yes	high
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	unknown†	yes	yes	yes	high

* High proportion of patients who prematurely discontinued the study and large differences in the proportion of these patients between the treatment groups

† information on blinding of assessors not available (patients were not blinded)

ITT = intention-to treat; MTX = methotrexate

Supplement Table 14: Risk of bias assessment for serious infections and mortality

Study	Risk of bias on study level	Blinding of outcome assessors	Appropriate application of ITT principle	Selective reporting unlikely	No other aspects generating bias	Risk of bias on outcome level
Abatacept + MTX vs. Adalimumab + MTX						
AMPLE	low	yes	yes	yes	yes	low
Adalimumab + MTX vs. Certolizumab pegol + MTX						
EXXELERATE	low	yes	yes	yes	yes	low

ITT = intention-to treat; MTX = methotrexate

Patient-relevant outcomes available for network meta-analyses

Supplement Table 15: Patient-relevant outcomes included in studies and availability for network meta-analyses

Biologic + MTX	Study	Outcome										
		Remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Serious adverse events	Infections	Pain (VAS)	Physical function (HAQ-DI)	Health-related quality of life (SF-36)	Fatigue*	Discontinuation due to adverse event	Serious infections	Mortality
Compared to Placebo + MTX												
Abatacept	AIM	●	●	●	●	●	●	●	●†	●	●	●
	ASSURE	-	-	○	○	○	○	-	-	○	○	●
	ATTEST	●	●	●	●	●	●	●	-	●	●	●
	IM101071	●	●	●	●	●	●	●	-	●	●	●
	IM101100	●	●	●	●	●	●‡	●	-	●	●	●
	IM101124	●	●	●	●	●	●	●	-	●	●	●
Adalimumab	ARMADA	●	●	●	●	○	●	●	●§	●	●	●
	August II	●	○	●	●	○	●	-	●§	●	●	●
	DE019	●	○	●	●	○	●	●	●§	●	●	●
	IM133001	●	-	●	-	○	●	-	-	●	-	●
	M02-556	●	●	○	○	○	○	-	-	○	○	●
	ORAL STANDARD	●	●	●	●	○	●	●	●§	●	●	●
	RA-BEAM	●	●	●	●	○	●	●	●§	●	●	●
	STAR	●	●	●	●	●	●	●	●§	●	●	●
Anakinra	990145	●	●	●	●	●	●	●	-	○	●	●
	990757	●	●	●	●	●	●	-	-	●	●	●
	20000198	●	●	●	●	-	-	-	-	○	●	●
Certolizumab pegol	CERTAIN	●	○	○	○	○	○	● / ○‖	●¶	○	○	●
	RAPID 1	●	○	●	●	○	●	●	●¶	●	●	●
	RAPID 2	●	○	●	●	○	●	●	●¶	●	●	●
	RA0025	●	●	●	●	○	●	●	-	●	●	●
Etanercept	ENCOURAGE	-	-	-	-	-	-	-	-	○	-	-
	TEMPO	●	●	●	●	○	●	-	-	●	●	●
	16.0014	●	●	●	●	●	●	-	-	●	●	●
Golimumab	C0524T28	●	●	●	●	-	●	●	●§	●	●	●
	GO-FORTH	●	●	●	●	-	●	-	-	●	-	●
	GO-FORWARD	●	●	-	●	-	●	●	●§	●	●	●
Infliximab	ATTRACT	●	●	●	●	●	●	●	●†	●	●	●
	P04280	-	-	●	●	-	-	●	-	●	●	-

Biologic + MTX	Study	Outcome										
		Remission (CDAI ≤ 2.8)	Low disease activity (CDAI ≤ 10)	Serious adverse events	Infections	Pain (VAS)	Physical function (HAQ-DI)	Health-related quality of life (SF-36)	Fatigue*	Discontinuation due to adverse event	Serious infections	Mortality
Compared to Placebo + MTX												
Tocilizumab	CWP-TCZ301	-	-	-	○	-	-	-	-	-	-	-
	LITHE	●	●	●	●	○	○	○	●§	●	●	●
	MEASURE	●	●	●	●	○	●	-	-	●	●	●
	OPTION	●	●	●	●	○	●	-	●§	●	●	●
	ROSE	●	●	●	●	-	-	-	-	●	●	●
	TOWARD	●	●	●	●	○	●	●	●§	●	●	●
	TRACE	●	●	●	●	●	●	-	●§	●	●	●
Direct evidence												
Abatacept vs. Adalimumab	AMPLE	●	●	●	●	●	●	●	●†	●	●	●
Certolizumab pegol vs. Adalimumab	EXXELERATE	●	○	-**	-**	○	●	●	●¶††	-**	-**	-**

● Data included in network meta-analysis;

○ Data not included in network meta-analysis (study excluded due to heterogeneity, inconsistency or results not robust in the sensitivity analysis for similarity assumptions);

- Data not available;

* Separate analyses were conducted for VAS / NRS and BRAF-MDQ / FACIT-Fatigue; † VAS; ‡ mHAQ; § FACIT-Fatigue; || physical component summary score / mental component summary score; ¶ NRS; ** only results after 2 years available, but not considered in the network meta-analysis (similarity with 24 or 52 weeks is not assumed); ††: BRAF-MDQ

BRAF-MDQ = Bristol rheumatoid arthritis fatigue - multidimensional questionnaire; CDAI = clinical disease activity index; FACIT-Fatigue = functional assessment of chronic illness therapy-fatigue; HAQ-DI = health assessment questionnaire – disability index; mHAQ = modified health assessment questionnaire; MTX = methotrexate; NRS = numerical rating scale; SF-36: short form 36 – health survey; VAS = visual analogue scale

Results for sensitivity analyses:

Results description for analyses of homogeneity, consistency and sensitivity analyses by outcome

Clinical remission (CDAI ≤ 2.8)

The data on clinical remission showed no relevant heterogeneity between studies in contrasts with more than 1 study and no relevant inconsistency in contrasts comprising a direct comparison was observed (see supplement tables 16 and 17). Sensitivity analyses investigating uncertainties for similarity assumptions showed robust results (see supplement tables 18 and 19).

Low disease activity (CDAI ≤ 10)

The data on low disease activity showed relevant heterogeneity between placebo-controlled studies for certolizumab pegol/MTX. Sensitivity analyses found the factor "deviant disease severity", which had been identified during the assessment of similarity, as a potential reason for heterogeneity. This resulted in the exclusion of the corresponding study containing this uncertainty (see supplement tables 18 and 19) and then resulted in homogeneous results for contrasts with certolizumab pegol/MTX. Relevant inconsistency was then identified within the closed loop certolizumab pegol-adalimumab-placebo (each combined with MTX). Sensitivity analyses did not find potential reasons for inconsistency. Thus, as the next step, studies with a high risk of bias within the affected loop were excluded (see Supplement Table 19). These exclusions also comprised the direct comparison within this loop of certolizumab pegol/MTX vs. adalimumab/MTX. Due to this exclusion, no further investigation of consistency was feasible. Only 1 study for certolizumab pegol/MTX vs. placebo/MTX remained for further analysis. For adalimumab/MTX vs. placebo/MTX, more than 1 study remained and no heterogeneity was found between these studies. Based on this study pool, sensitivity analyses due to uncertainties identified during the assessment of similarity were conducted. They were only applicable for the factor "unknown or deviant disease severity". For the other factors, the remaining study pool did not contain corresponding studies. The sensitivity analysis investigating the similarity factor "unknown or deviant disease severity" showed robust results (see supplement tables 18 and 19).

Pain

The data on pain showed relevant heterogeneity between placebo-controlled studies for abatacept/MTX, etanercept/MTX and tocilizumab/MTX. Sensitivity analyses found the factor "deviant disease severity", which had been identified during the assessment of similarity, as a potential reason for heterogeneity for abatacept/MTX and etanercept/MTX. This resulted in the exclusion of the corresponding studies containing this uncertainty and afterwards in homogeneous results for abatacept/MTX. Due to this exclusion, no further investigation of homogeneity was feasible for etanercept/MTX vs. placebo/MTX because only 1 study remained for further analysis. For tocilizumab/MTX, sensitivity analyses for factors identified during the assessment of similarity did not find potential reasons for heterogeneity. As a next

step, studies with a high risk of bias were excluded (excluded studies see Supplement table 19). This led to homogeneous results for tocilizumab/MTX. Relevant inconsistency was identified within the closed loop certolizumab pegol-adalimumab-placebo (each combined with MTX). Sensitivity analyses did not find potential reasons for inconsistency. As the next step, studies with high risk of bias within the affected loop were excluded (see Supplement Table 19). These exclusions comprised all studies with certolizumab pegol/MTX and the direct comparison of certolizumab pegol/MTX vs. adalimumab/MTX. Sensitivity analyses due to uncertainties during assessment of similarity were not applicable, since the corresponding studies had already been excluded in the investigations of homogeneity and consistency described above.

Physical function

The data on physical function showed no relevant heterogeneity between studies in contrasts with more than 1 study and no relevant inconsistency in contrasts comprising a direct comparison (see supplement tables 16 and 17). Results from sensitivity analyses investigating uncertainties for similarity assumptions were not robust when the factors "unknown or deviant disease severity" and "unknown proportion or 5-20 % of patients pretreated with biologics" were investigated. This led to the exclusion of a total of 4 placebo-controlled studies (see supplement tables 18 and 19). Further sensitivity analyses due to uncertainties during the assessment of similarity were not applicable, since the corresponding studies had already been excluded in the sensitivity analyses described above.

Serious adverse events

The data on serious adverse events showed no relevant heterogeneity between studies in contrasts with more than 1 study and no relevant inconsistency in contrasts comprising a direct comparison (see supplement tables 16 and 17). Results from sensitivity analyses investigating uncertainties for similarity assumptions were not robust when the factor "unknown or deviant disease severity" was investigated. This led to the exclusion of 3 placebo-controlled studies (Supplement Tables 18 and 19). Further sensitivity analyses due to uncertainties during assessment of similarity were not applicable, since either no factor applied to one of the studies or the corresponding studies had already been excluded in the sensitivity analysis described above.

Infections

The data on infections showed no relevant heterogeneity between studies in contrasts with more than 1 study and no relevant inconsistency in contrasts comprising a direct comparison (see supplement tables 16 and 17). Results from sensitivity analyses investigating uncertainties for similarity assumptions were not robust when investigating the factors "unknown or deviant disease severity" and "unknown proportion or 5-20% of patients pretreated with biologics". This led to the exclusion of 4 placebo-controlled studies (see Supplement Tables 18 and 19). Further sensitivity analyses due to uncertainties during the assessment of similarity were not applicable, since the corresponding studies had already been excluded in the sensitivity analyses described above.

Other outcomes

The data on quality of life, fatigue, serious infections and mortality showed no relevant heterogeneity between studies in contrasts with more than 1 study and no relevant inconsistency in contrasts comprising a direct comparison. Data on discontinuation due to adverse events showed relevant heterogeneity in contrasts with more than 1 study, which led to the exclusion of 2 studies. No relevant inconsistency in contrasts comprising a direct comparison for this outcome was shown.

Results for quality of life from sensitivity analyses investigating uncertainties for similarity assumptions were not robust when investigating the factor "unknown or deviant disease severity" for physical component summary score (PCS). The sensitivity analysis investigating the factor "unknown proportion or 5-20 % of patients pretreated with biologics" showed no robust results for the PCS and the mental component summary score (MCS). These results led to the exclusion of 2 placebo-controlled studies for PCS and 1 placebo-controlled study for MCS.

Results from sensitivity analyses investigating uncertainties for similarity assumptions for discontinuation due to adverse event and serious infections were not robust when investigating the factor "unknown or deviant disease severity". This led to the exclusion of 4 studies (discontinuation due to adverse event) and 3 studies (serious infections).

Results from sensitivity analyses investigating uncertainties for similarity assumptions for fatigue und mortality were robust when investigating the factor "unknown or deviant disease severity". For mortality, results were also robust when investigating the factor "insufficient information on disease severity or pretreatment".

Further sensitivity analyses due to uncertainties during the assessment of similarity were not applicable for these 5 outcomes, since either no factor applied to one of the studies or the corresponding studies had already been excluded in the sensitivity analyses described above.

Results for checks of homogeneity and consistency assumptions

Supplement Table 16: Results for the check of the homogeneity assumption

Biologic + MTX vs. Placebo + MTX	**Heterogeneity: p-values based on pairwise meta-analyses (Cochran's Q test) in preliminary analysis / in network meta-analysis (if study pool was modified)**												
							Health-related quality of life						
	Remission (CDAI ≤ 2.8)	**Low disease activity (CDAI ≤ 10)**	**Serious adverse events**	**Infections**	**Pain (VAS)**	**Physical function (HAQ-DI)**	**SF-36, PCS**	**SF-36, MCS**	**Fatigue (VAS / NRS)***	**Fatigue (BRAF-MDQ / FACIT-Fatigue)***	**Discontinuation due to adverse event**	**Serious infections**	**Mortality**
Abatacept	0.169	0.848	0.320 / 0.212	0.155 / 0.099	**0.012** / 0.380	0.286 / 0.287	0.923	0.821	n. c.	-†	0.313 / 0.217	0.564 / 0.480	0.978
Adalimumab	0.830	0.221 / 0.068	0.260 / 0.198	0.882 / 0.850	0.446 / n. c.	0.109 / 0.071	0.061	0.717	n. c.	0.617	0.401 / 0.309	0.218 / 0.204	0.996
Anakinra	0.689	0.823	0.946	0.140	0.864	0.882	n. c.	n. c.	-†	-†	**0.031** / n. c.	0.277	0.822
Certolizumab pegol	0.669	**0.002** / n. c.	0.282 / 0.706	0.124 / 0.581	0.481 / -†	0.065/ 0.661	0.468 / 0.282	0.429	0.172	n. c.	0.379 / 0.372	0.893 / 0.898	0.977
Etanercept	0.643	0.222	0.221	0,170	**0.003** / n. c.	0.960	- †	-†	-†	-†	0.921 / 0.712	0.844	0.829
Golimumab	0.785	0.669	0.888	0.472	-†	0.579	0.694	0.054	-†	0.924	0.103	0.791	0.988
Infliximab	n. c.	n. c.	0.897	0.960	n. c.	n. c.	0.378	0.839	n. c.	-†	0.164	0.593	n. c.
Tocilizumab	0.225	0.468	0.460	0.113 / 0.172	**0.042** / n. c.	0.539 / 0.398	0.103 / n. c.	0.183 / n. c.	-†	0.089	0.551	0.609	0.972

p-values shown in boldface indicate substantial heterogeneity ($p < 0.05$)

*Separate analyses were conducted for VAS / NRS and BRAF-MDQ / FACIT-Fatigue; † no data available for network meta-analysis

BRAF-MDQ = Bristol rheumatoid arthritis fatigue - multidimensional questionnaire; CDAI = clinical disease activity index; FACIT-Fatigue = functional assessment of chronic illness therapy-fatigue; HAQ-DI = health assessment questionnaire – disability index; MCS = mental component summary score; MTX = methotrexate; n. c. = not computable (one single study available); NRS = numerical rating scale; PCS = physical component summary score; SF-36 = short form 36 – health survey; VAS = visual analogue scale

Supplement Table 17: Results for the check of the consistency assumption

Comparison (treatment in combination with MTX)	**Inconsistency: p-values based on node-splitting in preliminary analysis / in network meta-analysis (if study pool was modified)**												
							Health related quality of life						
	Remission (CDAI ≤ 2.8)	**Low disease activity (CDAI ≤ 10)**	**Serious adverse events**	**Infections**	**Pain (VAS)**	**Physical function (HAQ-DI)**	**SF-36, PCS**	**SF-36, MCS**	**Fatigue (VAS / NRS)***	**Fatigue (BRAF-MDQ / FACIT-Fatigue)***	**Discontinuation due to adverse event**	**Serious infections**	**Mortality**
Abatacept – Adalimumab	0.970	0.462 / 0.730	0.857 / 0.755	0.169 / 0.163	0.507 / 0.627	0.499 / 0.691	0.769 / 0.771	0.971 / 0.971	0.228	n. c.	0.395 / 0.618	0.973 / 0.963	0.221
Abatacept – Placebo	0.970	0.462 / 0.730	0.857/ 0.755	0.169 / 0.163	0.507 / 0.627	0.499 / 0,691	0.769 / 0.771	0.971 / 0.971	0.228	n. c.	0.395 / 0.618	0.973 / 0.963	0.221
Adalimumab – Certolizumab pegol	0.875	**0.014** / n. c.	n. c.	n. c.	**0.023** / n. c.	0.203 / 0.069	0.835 / 0.822	0.462 / 0.462	0.228	n. c.	n. c.	n. c.	n. c.
Adalimumab – Placebo	0.919	0.333 / 0.730	0.857 / 0.755	0.169 / 0.163	0.225 / 0.627	0.596 / 0.241	0.949 / 0.944	0.578 / 0.578	n. c.	n. c.	0.395 / 0.618	0.973 / 0.963	0.221
Certolizumab pegol – Placebo	0.875	**0.014** / n. c.	n. c.	n. c.	**0.023** / n. c.	0.203 / 0.069	0.835 / 0.822	0.462 / 0.462	0.228	n. c.	n. c.	n. c.	n. c.

P-values shown in bold font indicate substantial inconsistency ($p < 0.05$)

*Separate analyses were conducted for VAS / NRS and BRAF-MDQ / FACIT-Fatigue;

BRAF-MDQ = Bristol rheumatoid arthritis fatigue - multidimensional questionnaire; CDAI = clinical disease activity index; FACIT-Fatigue = functional assessment of chronic illness therapy-fatigue; HAQ-DI = health assessment questionnaire – disability index; MCS = mental component summary score; MTX = methotrexate; n. c. = not computable (no direct comparison available); NRS = numerical rating scale; PCS = physical component summary score; SF-36 = short form 36 – health survey; VAS = visual analogue scale

Studies with uncertainties for similarity assumptions

Supplement Table 18: Studies with uncertainties explored in sensitivity analyses

Biologic + MTX	**Sensitivity analysis 1 (unknown or deviant disease severity)**	**Sensitivity analysis 2 (unknown proportion or 5-20 % of patients pretreated with biologics)**	**Sensitivity analysis 3 (insufficient information on disease severity or pretreatment)**
Abatacept	ASSURE	-	ASSURE
Adalimumab	M02-556	-	-
Certolizumab pegol	CERTAIN	-	-
Etanercept	ENCOURAGE	ENCOURAGE	ENCOURAGE
Tocilizumab	-	CWP-TCZ301	CWP-TCZ301
		LITHE*	

* Patients pretreated with biologics were included for the following outcomes only: physical function (HAQ-DI) and health-related quality of life (SF-36)

- No studies with uncertainties

HAQ-DI = health assessment questionnaire – disability index; MTX = methotrexate; SF 36 = short form 36 – health survey

Studies excluded in sensitivity analyses

Supplement Table 19: Studies permanently excluded after assessments of homogeneity or consistency and sensitivity analyses conducted to check assumptions of similarity

Outcome	Studies excluded at the end of analysis step (reasons for exclusion)			
	Preliminary analysis	**Sensitivity analysis 1**	**Sensitivity analysis 2**	**Sensitivity analysis 3**
Clinical remission (CDAI ≤ 2.8)	-*	-*	-†	-†
Low disease activity (CDAI ≤ 10)	CERTAIN (H)‡	-*	-†	-†
	August II, DE019, RAPID 1, RAPID 2, EXXELERATE (I)§			
Serious adverse events	-*	ASSURE, M02-556, CERTAIN (R)	-†	-†
Infections	-*	ASSURE, M02-556, CERTAIN (R)	CWP-TCZ301 (R)	-†
Pain (VAS)	ASSURE (H)‡	-†	-†	-†
	TEMPO (H)‖			
	LITHE, MEASURE, OPTION, TOWARD (H)§			
	ARMADA, August II, DE019, IM133001, M02-556, ORAL STANDARD, RA-BEAM, CERTAIN, RAPID 1, RAPID 2, RA0025, EXXELERATE (I)§			
Physical function (HAQ-DI)	-*	ASSURE, M02-556, CERTAIN (R)	LITHE (R)	-†
Health-related quality of life (SF-36, physical component summary score)	-*	CERTAIN (R)	LITHE (R)	-†
Health-related quality of life (SF-36, mental component summary score)	-*	-*	LITHE (R)	-†
Fatigue (VAS / NRS)	-*	-*	-†	-†
Fatigue (FACIT-Fatigue / BRAF-MDQ)	-*	-†	-†	-†

Outcome	Studies excluded at the end of analysis step (reasons for exclusion)			
	Preliminary analysis	**Sensitivity analysis 1**	**Sensitivity analysis 2**	**Sensitivity analysis 3**
Discontinuation due to adverse event	990145, 20000198 (H)§	ASSURE, M02-556, CERTAIN, ENCOURAGE (R)	-†	-†
Serious infections	-*	ASSURE, M02-556, CERTAIN (R)	-†	-†
Mortality	-*	-*	-†	-*

* No studies excluded after this analysis (analysis shows robust results)
† Analysis not performed (no studies with characteristics of interest in the study pool of interest)
‡ Majority of patients included in the study had less severe rheumatoid arthritis
§ High risk of bias on the outcome level in these studies
|| Majority of patients included in the study had more severe rheumatoid arthritis

Reasons for permanent exclusion: heterogeneity (H), inconsistency (I), results not robust in the sensitivity analysis compared to the previous analysis step (R)

Sensitivity analysis 1: majority of the patients had less severe rheumatoid arthritis or severity of rheumatoid arthritis was unclear

Sensitivity analysis 2: about 5-20 % of the patients were pretreated with biologics or proportion of pretreated patients was unclear

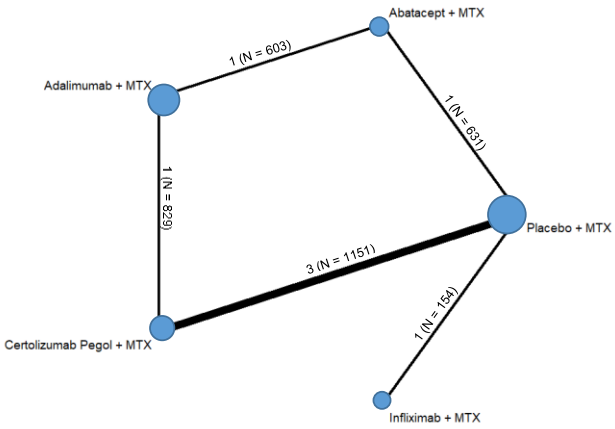
Sensitivity analysis 3: information on pretreatment of the patients or severity of rheumatoid arthritis not available

BRAF-MDQ = Bristol rheumatoid arthritis fatigue - multidimensional questionnaire; CDAI = clinical disease activity index; FACIT-Fatigue = functional assessment of chronic illness therapy-fatigue; HAQ-DI = health assessment questionnaire – disability index; NRS = numerical rating scale; SF 36 = short form 36 – health survey; VAS = visual analogue scale

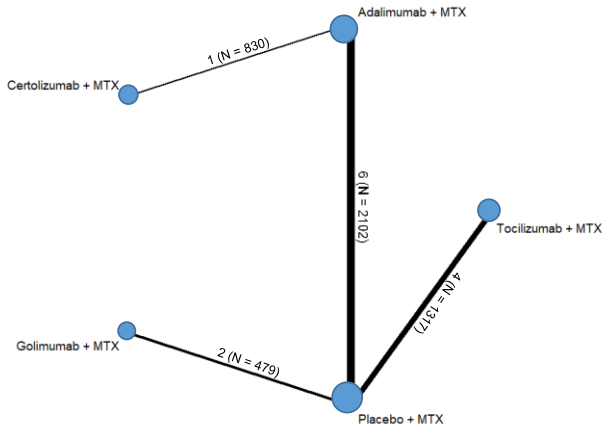
Results for final network meta-analysis

Supplement Figure 1: Network plots of treatment comparisons for the outcomes fatigue and health-related quality of life

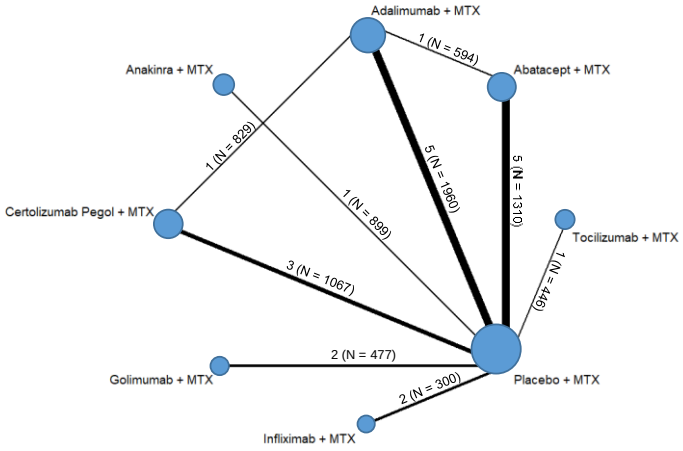
A Fatigue (VAS / NRS)



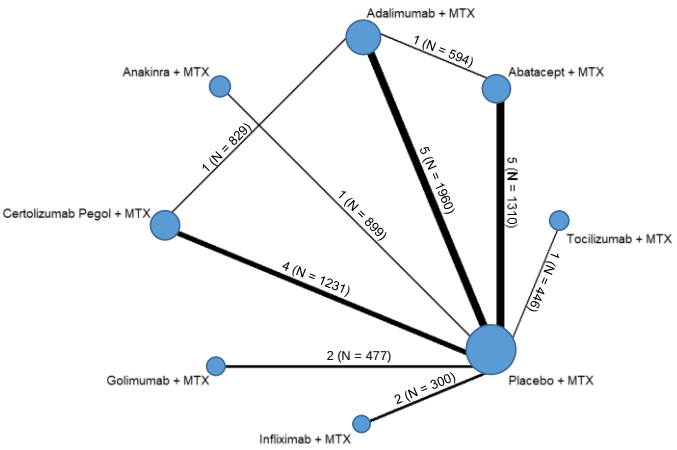
B Fatigue (BRAF-MDQ / FACIT-Fatigue)



C HRQoL (SF-36, PCS)



D HRQoL (SF-36, MCS)

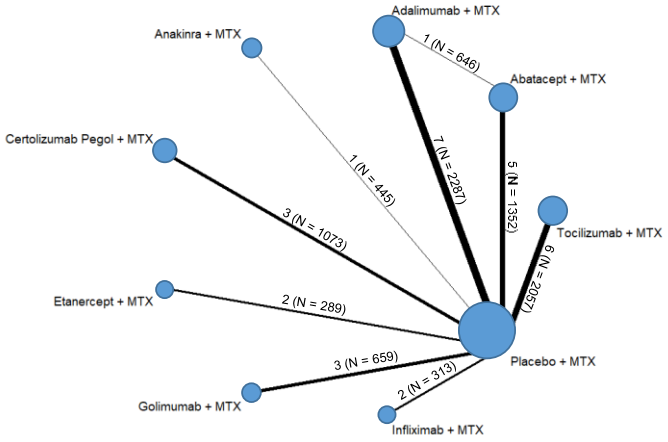


Network plots include the number of trials and the number of included patients for each comparison.

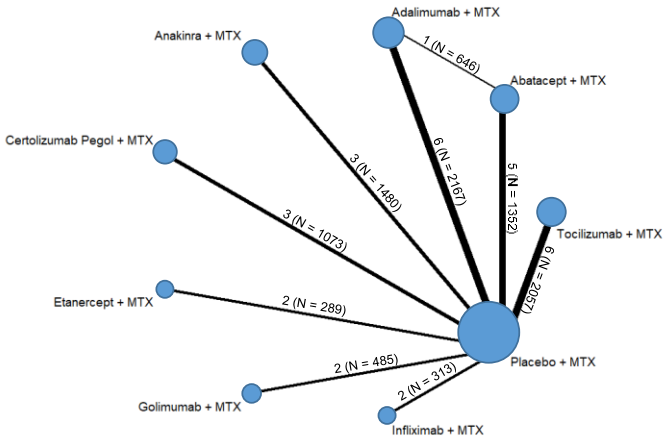
BRAF-MDQ = Bristol rheumatoid arthritis fatigue - multidimensional questionnaire; FACIT-Fatigue = functional assessment of chronic illness therapy-fatigue; HRQoL = health-related quality of life; MCS = mental component summary score; MTX = methotrexate; NRS = numerical rating scale; PCS = physical component summary score; SF-36: short form 36 health survey; VAS = visual analogue scale

Supplement Figure 2: Network plots of treatment comparisons for the outcomes discontinuation due to adverse event, serious infections and mortality

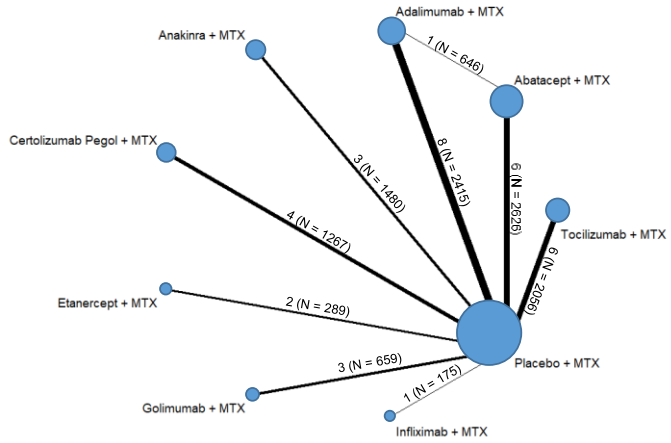
A Discontinuation due to adverse event



B Serious infections



C Mortality



Network plots include the number of trials and the number of included patients for each comparison.

MTX = methotrexate; N = number of included patients

Supplement Table 20: Network meta-analysis estimates for each comparison of biologic treatments for the following outcomes: remission, low disease activity, serious adverse events and infections

Comparison (treatment in combination with MTX)	**Remission (CDAI ≤ 2.8) RR [95% CI]**	**Low disease activity (CDAI ≤ 10) RR [95% CI]**	**Serious adverse events RR [95% CI]**	**Infections RR [95% CI]**
Abatacept vs.				
Adalimumab	0.83 [0.60; 1.16]	0.94 [0.82; 1.08]	1.04 [0.74; 1.46]	0.94 [0.82; 1.07]
Anakinra	3.00 [0.94; 9.61]	**1.46 [1.01; 2.09]**	0.99 [0.64; 1.52]	1.09 [0.89; 1.33]
Certolizumab pegol	0.75 [0.50; 1.13]	0.93 [0.39; 2.24]	**0.42 [0.23; 0.78]**	**0.73 [0.56; 0.95]**
Etanercept	0.63 [0.16; 2.49]	1.20 [0.81; 1.78]	1.02 [0.51; 2.04]	1.12 [0.88; 1.42]
Golimumab	0.64 [0.27; 1.50]	1.01 [0.75; 1.36]	0.40 [0.10; 1.57]	1.08 [0.79; 1.46]
Infliximab	0.59 [0.07; 5.11]	0.51 [0.22; 1.19]	1.65 [0.83; 3.25]	0.84 [0.61; 1.15]
Tocilizumab	1.11 [0.55; 2.22]	0.84 [0.65; 1.08]	0.78 [0.47; 1.30]	0.99 [0.81; 1.20]
Adalimumab vs.				
Abatacept	1.20 [0.86; 1.67]	1.06 [0.93; 1.22]	0.96 [0.68; 1.34]	1.07 [0.93; 1.22]
Anakinra	**3.60 [1.16; 11.22]**	**1.55 [1.08; 2.21]**	0.95 [0.60; 1.49]	1.17 [0.96; 1.41]
Certolizumab pegol	0.90 [0.70; 1.16]	0.99 [0.41; 2.38]*	**0.41 [0.22; 0.75]**	0.78 [0.61; 1.01]
Etanercept	0.75 [0.19; 2.93]	1.27 [0.86; 1.88]	0.97 [0.48; 1.98]	1.20 [0.95; 1.51]
Golimumab	0.77 [0.34; 1.73]	1.07 [0.80; 1.43]	0.38 [0.10; 1.51]	1.15 [0.85; 1.56]
Infliximab	0.71 [0.08; 6.05]	0.54 [0.23; 1.26]	1.58 [0.79; 3.15]	0.89 [0.65; 1.22]
Tocilizumab	1.33 [0.69; 2.55]	0.89 [0.70; 1.14]	0.75 [0.44; 1.26]	1.05 [0.87; 1.27]
Anakinra vs.				
Abatacept	0.33 [0.10; 1.07]	**0.69 [0.48; 0.99]**	1.01 [0.66; 1.56]	0.92 [0.75; 1.12]
Adalimumab	**0.28 [0.09; 0.86]**	**0.65 [0.45; 0.92]**	1.06 [0.67; 1.66]	0.86 [0.71; 1.04]
Certolizumab pegol	**0.25 [0.08; 0.79]**	0.64 [0.25; 1.61]	**0.43 [0.23; 0.81]**	**0.67 [0.51; 0.89]**
Etanercept	0.21 [0.04; 1.16]	0.82 [0.50; 1.34]	1.03 [0.50; 2.11]	1.03 [0.79; 1.33]
Golimumab	**0.21 [0.06; 0.81]**	0.69 [0.46; 1.05]	0.40 [0.10; 1.61]	0.99 [0.71; 1.36]
Infliximab	0.20 [0.02; 2.14]	**0.35 [0.14; 0.86]**	1.67 [0.82; 3.37]	0.77 [0.55; 1.07]
Tocilizumab	0.37 [0.11; 1.27]	**0.58 [0.39; 0.85]**	0.79 [0.46; 1.35]	0.90 [0.72; 1.12]
Certolizumab pegol vs.				
Abatacept	1.33 [0.89; 2.00]	1.08 [0.45; 2.60]	**2.36 [1.29; 4.31]**	**1.37 [1.06; 1.77]**
Adalimumab	1.11 [0.86; 1.43]	1.01 [0.42; 2.44]†	**2.46 [1.33; 4.56]**	1.28 [0.99; 1.65]
Anakinra	**3.99 [1.26; 12.63]**	1.57 [0.62; 3.96]	**2.33 [1.24; 4.38]**	**1.49 [1.13; 1.97]**
Etanercept	0.84 [0.21; 3.28]	1.29 [0.50; 3.30]	**2.39 [1.04; 5.52]**	**1.53 [1.12; 2.08]**
Golimumab	0.85 [0.37; 1.96]	1.09 [0.44; 2.68]	0.94 [0.22; 3.99]	**1.47 [1.02; 2.12]**
Infliximab	0.78 [0.09; 6.76]	0.55 [0.16; 1.82]	**3.88 [1.71; 8.82]**	1.14 [0.79; 1.66]
Tocilizumab	1.47 [0.75; 2.90]	0.91 [0.37; 2.20]	1.84 [0.93; 3.65]	**1.35 [1.02; 1.77]**

Comparison (treatment in combination with MTX)	Remission (CDAI ≤ 2.8) RR [95% CI]	Low disease activity (CDAI ≤ 10) RR [95% CI]	Serious adverse events RR [95% CI]	Infections RR [95% CI]
Etanercept vs.				
Abatacept	1.59 [0.40; 6.34]	0.83 [0.56; 1.24]	0.98 [0.49; 1.98]	0.89 [0.70; 1.13]
Adalimumab	1.33 [0.34; 5.15]	0.79 [0.53; 1.16]	1.03 [0.51; 2.09]	0.84 [0.66; 1.06]
Anakinra	4.78 [0.86; 26.57]	1.22 [0.75; 1.98]	0.97 [0.47; 2.00]	0.98 [0.75; 1.26]
Certolizumab pegol	1.20 [0.30; 4.71]	0.78 [0.30; 1.98]	**0.42 [0.18; 0.96]**	**0.65 [0.48; 0.89]**
Golimumab	1.02 [0.22; 4.67]	0.84 [0.54; 1.31]	0.39 [0.09; 1.74]	0.96 [0.68; 1.36]
Infliximab	0.94 [0.08; 11.44]	0.42 [0.17; 1.06]	1.62 [0.66; 3.95]	0.75 [0.52; 1.07]
Tocilizumab	1.76 [0.42; 7.44]	0.70 [0.46; 1.06]	0.77 [0.36; 1.66]	0.88 [0.68; 1.14]
Golimumab vs.				
Abatacept	1.56 [0.67; 3.66]	0.99 [0.74; 1.33]	2.51 [0.64; 9.85]	0.93 [0.68; 1.26]
Adalimumab	1.30 [0.58; 2.93]	0.93 [0.70; 1.24]	2.61 [0.66; 10.34]	0.87 [0.64; 1.18]
Anakinra	**4.68 [1.24; 17.66]**	1.44 [0.96; 2.17]	2.48 [0.62; 9.85]	1.01 [0.73; 1.40]
Certolizumab pegol	1.17 [0.51; 2.70]	0.92 [0.37; 2.27]	1.06 [0.25; 4.50]	**0.68 [0.47; 0.98]**
Etanercept	0.98 [0.21; 4.48]	1.19 [0.76; 1.84]	2.54 [0.58; 11.24]	1.04 [0.73; 1.47]
Infliximab	0.92 [0.10; 8.75]	0.50 [0.21; 1.21]	4.12 [0.94; 18.07]	0.78 [0.52; 1.17]
Tocilizumab	1.73 [0.67; 4.45]	0.83 [0.61; 1.15]	1.95 [0.48; 7.97]	0.92 [0.66; 1.26]
Infliximab vs.				
Abatacept	1.70 [0.20; 14.81]	1.97 [0.84; 4.63]	0.61 [0.31; 1.20]	1.19 [0.87; 1.64]
Adalimumab	1.42 [0.17; 12.15]	1.85 [0.79; 4.34]	0.63 [0.32; 1.27]	1.12 [0.82; 1.53]
Anakinra	5.11 [0.47; 55.76]	**2.87 [1.17; 7.06]**	0.60 [0.30; 1.21]	1.30 [0.93; 1.82]
Certolizumab pegol	1.28 [0.15; 11.05]	1.83 [0.55; 6.12]	**0.26 [0.11; 0.59]**	0.87 [0.60; 1.27]
Etanercept	1.07 [0.09; 13.05]	2.36 [0.95; 5.89]	0.62 [0.25; 1.50]	1.34 [0.93; 1.92]
Golimumab	1.09 [0.11; 10.40]	1.99 [0.83; 4.78]	0.24 [0.06; 1.06]	1.29 [0.86; 1.93]
Tocilizumab	1.88 [0.21; 17.03]	1.66 [0.70; 3.92]	0.47 [0.22; 1.01]	1.18 [0.84; 1.64]
Tocilizumab vs.				
Abatacept	0.90 [0.45; 1.82]	1.19 [0.92; 1.53]	1.28 [0.77; 2.13]	1.01 [0.84; 1.23]
Adalimumab	0.75 [0.39; 1.44]	1.12 [0.88; 1.43]	1.34 [0.79; 2.26]	0.95 [0.79; 1.15]
Anakinra	2.71 [0.79; 9.31]	**1.73 [1.18; 2.53]**	1.27 [0.74; 2.17]	1.11 [0.89; 1.38]
Certolizumab pegol	0.68 [0.35; 1.33]	1.10 [0.45; 2.69]	0.54 [0.27; 1.08]	**0.74 [0.56; 0.98]**
Etanercept	0.57 [0.13; 2.39]	1.42 [0.94; 2.15]	1.30 [0.60; 2.81]	1.14 [0.88; 1.47]
Golimumab	0.58 [0.22; 1.49]	1.20 [0.87; 1.65]	0.51 [0.13; 2.09]	1.09 [0.79; 1.51]
Infliximab	0.53 [0.06; 4.80]	0.60 [0.25; 1.43]	2.11 [0.99; 4.48]	0.85 [0.61; 1.18]

Effects are shown in both directions and therefore listed twice; effects in bold font represent an added or less benefit or harm for the first biologic; effect estimates are highlighted in grey if direct evidence was incorporated.

* Direct evidence excluded from the network meta-analysis due to inconsistency: adalimumab vs. certolizumab pegol: RR [95% CI] : 0.95 [0.84; 1.08]

† Direct evidence excluded from the network meta-analysis due to inconsistency: certolizumab pegol vs adalimumab: RR [95% CI]: 1.05 [0.93; 1.19]

CDAI = clinical disease activity index; CI = confidence interval; MTX = methotrexate; RR = risk ratio

Supplement Table 21: Network meta-analysis estimates for pain (VAS) and physical function (HAQ-DI) for each comparison of biologic treatments

Comparison (treatment in combination with MTX)	**Pain (VAS, mm)**		**Physical function (HAQ-DI)**	
	MD [95% CI]	**SMD [95% CI]**	**MD [95% CI]**	**SMD [95% CI]**
Abatacept vs.				
Adalimumab	−3.56 [−6.81; −0.31]	−0.13 [−0.26; 0.00]	0.00 [−0.07; 0,08]	n/a
Anakinra	**−12.24 [−16.37; −8.11]**	**−0.50 [−0.65; −0.34]**	−0.18 [−0.28; −0.08]	−0.25 [−0.45; −0.04]
Certolizumab pegol	-*	n/a	0.06 [−0.03; 0.16]	n/a
Etanercept	7.67 [−2.83; 18.18]	n/a	0.02 [−0.18; 0.22]	n/a
Golimumab	-†	n/a	0.08 [−0.04; 0.20]	n/a
Infliximab	−9.33 [−18.08; −0.57]	−0.38 [−0.71; −0.05]	−0.27 [−0.51; −0.03]	−0.46 [−0.82; −0.09]
Tocilizumab	4.47 [−5.56; 14.51]	n/a	0.03 [−0.08; 0.15]	n/a
Adalimumab vs.				
Abatacept	3.56 [0.31; 6.81]	0.13 [0.00; 0.26]	−0.00 [−0.08; 0.07]	n/a
Anakinra	−8.68 [−13.40; −3.97]	−0.37 [−0.55; −0.19]	−0.18 [−0.27; −0.09]	−0.28 [−0.47; −0.09]
Certolizumab pegol	-*	n/a	0.06 [−0.01; 0.13]	n/a
Etanercept	11.23 [0.49; 21.98]	0.51 [0.02; 1.00]	0.02 [−0.17; 0.21]	n/a
Golimumab	-†	n/a	0.08 [−0.03; 0.18]	n/a
Infliximab	−5.77 [−14.81; 3.28]	n/a	−0.27 [−0.51; −0.04]	−0.49 [−0.85; −0.13]
Tocilizumab	8.03 [−2.26; 18.32]	n/a	0.03 [−0.08; 0.14]	n/a
Anakinra vs.				
Abatacept	**12.24 [8.11; 16.37]**	**0.50 [0.34; 0.65]**	0.18 [0.08; 0.28]	0.25 [0.04; 0.45]
Adalimumab	8.68 [3.97; 13.40]	0.37 [0.19; 0.55]	0.18 [0.09; 0.27]	0.28 [0.09; 0.47]
Certolizumab pegol	-*	n/a	0.24 [0.14; 0.34]	0.41 [0.199; 0.63]
Etanercept	19.92 [9.23; 30.60]	0.88 [0.40; 1.36]‡	0.20 [−0.001; 0.40]	n/a
Golimumab	-†	n/a	0.26 [0.13; 0.38]	0.40 [0.15; 0.64]
Infliximab	2.92 [−6.06; 11.89]	n/a	−0.09 [−0.34; 0.15]	n/a
Tocilizumab	**16.72 [6.49; 26.94]**	**0.71 [0.27; 1.14]**	0.21 [0.09; 0.33]	0.29 [0.05; 0.53]
Certolizumab pegol vs.				
Abatacept	-*	n/a	−0.06 [−0.16; 0.03]	n/a
Adalimumab	-*	n/a	−0.06 [−0.13; 0.01]	n/a
Anakinra	-*	n/a	−0.24 [−0.34; −0.14]	−0.41 [−0.63; −0.199]
Etanercept	-*	n/a	−0.04 [−0.24; 0.16]	n/a
Golimumab	-†	n/a	0.01 [−0.10; 0.13]	n/a
Infliximab	-*	n/a	−0.33 [−0.57; −0.09]	−0.62 [−1.00; −0.25]‡
Tocilizumab	-*	n/a	−0.03 [−0.15; 0.09]	n/a

Comparison (treatment in combination with MTX)	Pain (VAS, mm)		Physical function (HAQ-DI)	
	MD [95% CI]	**SMD [95% CI]**	**MD [95% CI]**	**SMD [95% CI]**
Etanercept vs.				
Abatacept	−7.67 [−18.18; 2.83]	n/a	−0.02 [−0.22; 0.18]	n/a
Adalimumab	−11.23 [−21.98; −0.49]	−0.51 [−1.00; −0.02]	−0.02 [−0.21; 0.17]	n/a
Anakinra	−19.92 [−30.60; −9.23]	−0.88 [−1.36; −0.40]‡	−0.20 [−0.40; 0.001]	n/a
Certolizumab pegol	-*	n/a	0.04 [−0.16; 0.24]	n/a
Golimumab	-†	n/a	0.06 [−0.16; 0.27]	n/a
Infliximab	−17.00 [−30.18; −3.82]	−0.76 [−1.33; −0.2002]‡	−0.29 [−0.59; 0.004]	n/a
Tocilizumab	−3.20 [−17.26; 10.86]	n/a	0.01 [−0.20; 0.22]	n/a
Golimumab vs.				
Abatacept	-†	n/a	−0.08 [−0.20; 0.04]	n/a
Adalimumab	-†	n/a	−0.08 [−0.18; 0.03]	n/a
Anakinra	-†	n/a	−0.26 [−0.38; −0.13]	−0.40 [−0.64; −0.15]
Certolizumab pegol	-†	n/a	−0.01 [−0.13; 0.1]	n/a
Etanercept	-†	n/a	−0.06 [−0.27; 0.16]	n/a
Infliximab	-†	n/a	−0.35 [−0.60; −0.10]	−0.61 [−1.00; −0.22]‡
Tocilizumab	-†	n/a	−0.04 [−0.18; 0.09]	n/a
Infliximab vs.				
Abatacept	9.33 [0.57; 18.08]	0.38 [0.05; 0.71]	0.27 [0.03; 0.51]	0.46 [0.09; 0.82]
Adalimumab	5.77 [−3.28; 14.81]	n/a	0.27 [0.04; 0.51]	0.49 [0.13; 0.85]
Anakinra	−2.92 [−11.89; 6.06]	n/a	0.09 [−0.15; 0.34]	n/a
Certolizumab pegol	-*	n/a	0.33 [0.09; 0.57]	0.62 [0.25; 1.00]‡
Etanercept	17.00 [3.82; 30.18]	0.76 [0.2002; 1.33]‡	0.29 [−0.004; 0.59]	n/a
Golimumab	-†	n/a	0.35 [0.10; 0.60]	0.61 [0.22; 1.00]‡
Tocilizumab	13.80 [0.99; 26.61]	0.59 [0.07; 1.12]	0.30 [0.05; 0.55]	0.50 [0.11; 0.89]
Tocilizumab vs.				
Abatacept	−4.47 [−14.51; 5.56]	n/a	−0.03 [−0.15; 0.08]	n/a
Adalimumab	−8.03 [−18.32; 2.26]	n/a	−0.03 [−0.14; 0.08]	n/a
Anakinra	**−16.72 [−26.94; −6.49]**	**−0.71 [−1.14; −0.27]**	−0.21 [−0.33; −0.09]	−0.29 [−0.53; −0.05]
Certolizumab pegol	-*	n/a	0.03 [−0.09; 0.15]	n/a
Etanercept	3.20 [−10.86; 17.26]	n/a	−0.01 [−0.22; 0.20]	n/a
Golimumab	-†	n/a	0.04 [−0.09; 0.18]	n/a
Infliximab	−13.80 [−26.61; −0.99]	−0.59 [−1.12; −0.07]	−0.30 [−0.55; −0.05]	−0.50 [−0.89; −0.11]

Effects are shown in both directions and are therefore listed twice; effects in bold font represent an added or less benefit or harm for the first biologic (negative values for MD or SMD = improvement for the first biologic); effect estimates are highlighted in grey if direct evidence was incorporated.

* Data excluded during assessment of homogeneity and consistency; † no study data available; ‡ data not interpreted as added or less benefit (indirect comparison supported by only 1 trial with a high risk of bias for at least 1 biologic)

CI = confidence interval; HAQ-DI = health assessment questionnaire – disability index; MD = mean difference; MTX = methotrexate; n/a = not applicable; SMD = standardized mean difference (Hedges' g); VAS = visual analogue scale

Supplement Table 22: Network meta-analysis estimates for each comparison of biologic treatments for health-related quality of life and fatigue

Comparison (treatment in combination with MTX)	**SF-36 PCS**		**SF-36 MCS**		**Fatigue VAS / NRS**		**Fatigue BRAF-MDQ / FACIT-Fatigue***
	MD [95% CI]	**SMD [95% CI]**	**MD [95% CI]**	**SMD [95% CI]**	**MD [95% CI]**	**SMD [95% CI]**	**SMD [95% CI]**
Abatacept vs.							
Adalimumab	0.50 [−0.43; 1.42]	n/a	1.34 [0.32; 2.35]	0.15 [0.04; 0.25]	−0.06 [−5.88; 5.76]	n/a	-†
Anakinra	2.73 [1.20; 4.27]	0.33 [0.17; 0.50]	2.50 [0.75; 4.24]	0.26 [0.09; 0.43]	-†	n/a	-†
Certolizumab pegol	1.12 [−0.14; 2.37]	n/a	0.87 [−0.54; 2.28]	n/a	2.02 [−4.23; 8.27]	n/a	-†
Etanercept	-†	n/a	-†	n/a	-†	n/a	-†
Golimumab	−1.01 [−2.59; 0.57]	n/a	0.12 [−2.03; 2.28]	n/a	-†	n/a	-†
Infliximab	0.35 [−1.82; 2.52]	n/a	2.76 [−0.15; 5.67]	n/a	−1.56 [−12.83; 9.70]	n/a	-†
Tocilizumab	−0.29 [−2.29; 1.72]	n/a	0.49 [−2.02; 3.00]	n/a	-†	n/a	-†
Adalimumab vs.							
Abatacept	−0.50 [−1.42; 0.43]	n/a	−1.34 [−2.35; −0.32]	−0.15 [−0.25; −0.04]	0.06 [−5.76; 5.88]	n/a	-†
Anakinra	2.24 [0.80; 3.68]	0.28 [0.13; 0.43]	1.16 [−0.50; 2.81]	n/a	-†	n/a	-†
Certolizumab pegol	0.62 [−0.34; 1.58]	n/a	−0.47 [−1.60; 0.66]	n/a	2.08 [−3.59; 7.75]	n/a	−0.04 [−0.20; 0.12]
Etanercept	-†	n/a	-†	n/a	-†	n/a	-†
Golimumab	−1.51 [−3.00; −0.01]	−0.27 [−0.48; −0.07]	−1.21 [−3.30; 0.87]	n/a	-†	n/a	−0.18 [−0.39; 0.04]
Infliximab	−0.14 [−2.25; 1.96]	n/a	1.42 [−1.44; 4.28]	n/a	−1.5 [−12.92; 9.92]	n/a	-†
Tocilizumab	−0.78 [−2.72; 1.15]	n/a	−0.85 [−3.30; 1.60]	n/a	-†	n/a	0.02 [−0.13; 0.17]

Comparison (treatment in combination with MTX)	SF-36 PCS		SF-36 MCS		Fatigue VAS / NRS		Fatigue BRAF-MDQ / FACIT-Fatigue*
	MD [95% CI]	SMD [95% CI]	MD [95% CI]	SMD [95% CI]	MD [95% CI]	SMD [95% CI]	SMD [95% CI]
Anakinra vs.							
Abatacept	−2.73 [−4.27; −1.20]	−0.33 [−0.50; −0.17]	−2.50 [−4.24; −0.75]	−0.26 [−0.43; −0.09]	-†	n/a	-†
Adalimumab	−2.24 [−3.68; −0.80]	−0.28 [−0.43; −0.13]	−1.16 [−2.81; 0.50]	n/a	-†	n/a	-†
Certolizumab pegol	−1.62 [−3.27; 0.03]	n/a	−1.63 [−3.51; 0.26]	n/a	-†	n/a	-†
Etanercept	-†	n/a	-†	n/a	-†	n/a	-†
Golimumab	**−3.74 [−5.61; −1.88]**	**−0.56 [−0.78; −0.33]**	−2.37 [−4.82; 0.08]	n/a	-†	n/a	-†
Infliximab	−2.38 [−4.76; −0.004]	−0.28 [−0.54; −0.01]	0.26 [−2.87; 3.40]	n/a	-†	n/a	-†
Tocilizumab	−3.02 [−5.25; −0.79]	−0.34 [−0.58; −0.10]	−2.01 [−4.78; 0.76]	n/a	-†	n/a	-†
Certolizumab pegol vs.							
Abatacept	−1.12 [−2.37; 0.14]	n/a	−0.87 [−2.28; 0.54]	n/a	−2.02 [−8.27; 4.23]	n/a	-†
Adalimumab	−0.62 [−1.58; 0.34]	n/a	0.47 [−0.66; 1.60]	n/a	−2.08 [−7.75; 3.59]	n/a	0.04 [−0.12; 0.20]
Anakinra	1.62 [−0.03; 3.27]	n/a	1.63 [−0.26; 3.51]	n/a	-†	n/a	-†
Etanercept	-†	n/a	-†	n/a	-†	n/a	-†
Golimumab	−2.13 [−3.82; −0.44]	−0.40 [−0.61; −0.19]	−0.74 [−3.02; 1.53]	n/a	-†	n/a	−0.14 [−0.41; 0.13]
Infliximab	−0.76 [−3.01; 1.48]	n/a	1.89 [−1.11; 4.88]	n/a	−3.58 [−13.97; 6.8]	n/a	-†
Tocilizumab	−1.40 [−3.49; 0.69]	n/a	−0.38 [−2.99; 2.23]	n/a	-†	n/a	0.06 [−0.16; 0.28]
Etanercept vs.							
Abatacept	-†	n/a	-†	n/a	-†	n/a	-†
Adalimumab	-†	n/a	-†	n/a	-†	n/a	-†
Anakinra	-†	n/a	-†	n/a	-†	n/a	-†
Certolizumab pegol	-†	n/a	-†	n/a	-†	n/a	-†
Golimumab	-†	n/a	-†	n/a	-†	n/a	-†
Infliximab	-†	n/a	-†	n/a	-†	n/a	-†
Tocilizumab	-†	n/a	-†	n/a	-†	n/a	-†

Comparison (treatment in combination with MTX)	SF-36 PCS		SF-36 MCS		Fatigue VAS / NRS		Fatigue BRAF-MDQ / FACIT-Fatigue*
	MD [95% CI]	SMD [95% CI]	MD [95% CI]	SMD [95% CI]	MD [95% CI]	SMD [95% CI]	SMD [95% CI]
Golimumab vs.							
Abatacept	1.01 [−0.57; 2.59]	n/a	−0.12 [−2.28; 2.03]	n/a	-†	n/a	-†
Adalimumab	1.51 [0.01; 3.00]	0.27 [0.07; 0.48]	1.21 [−0.87; 3.30]	n/a	-†	n/a	0.18 [−0.04; 0.39]
Anakinra	**3.74 [1.88; 5.61]**	**0.56 [0.33; 0.78]**	2.37 [−0.08; 4.82]	n/a	-†	n/a	-†
Certolizumab pegol	2.13 [0.44; 3.82]	0.40 [0.19; 0.61]	0.74 [−1.53; 3.02]	n/a	-†	n/a	0.14 [−0.13; 0.41]
Etanercept	-†	n/a	-†	n/a	-†	n/a	-†
Infliximab	1.36 [−1.05; 3.77]	n/a	2.63 [−0.75; 6.01]	n/a	-†	n/a	-†
Tocilizumab	0.72 [−1.54; 2.99]	n/a	0.36 [−2.68; 3.40]	n/a	-†	n/a	0.20 [−0.03; 0.43]
Infliximab vs.							
Abatacept	−0.35 [−2.52; 18.2]	n/a	−2.76 [−5.67; 0.15]	n/a	1.56 [−9.70; 12.83]	n/a	-†
Adalimumab	0.14 [−1.96; 2.25]	n/a	−1.42 [−4.28; 1.44]	n/a	1.5 [−9.92; 12.92]	n/a	-†
Anakinra	2.38 [0.004; 4.76]	0.28 [0.01; 0.54]	−0.26 [−3.40; 2.87]	n/a	-†	n/a	-†
Certolizumab pegol	0.76 [−1.48; 3.01]	n/a	−1.89 [−4.88; 1.11]	n/a	3.58 [−6.8; 13.97]	n/a	-†
Etanercept	-†	n/a	-†	n/a	-†	n/a	-†
Golimumab	−1.36 [−3.77; 1.05]	n/a	−2.63 [−6.01; 0.75]	n/a	-†	n/a	-†
Tocilizumab	−0.64 [−3.34; 2.07]	n/a	−2.27 [−5.89; 1.35]	n/a	-†	n/a	-†
Tocilizumab vs.							
Abatacept	0.29 [−1.72; 2.29]	n/a	−0.49 [−3.00; 2.02]	n/a	-†	n/a	-†
Adalimumab	0.78 [−1.15; 2.72]	n/a	0.85 [−1.60; 3.30]	n/a	-†	n/a	−0.02 [−0.17; 0.13]
Anakinra	3.02 [0.79; 5.25]	0.34 [0.10; 0.58]	2.01 [−0.76; 4.78]	n/a	-†	n/a	-†
Certolizumab pegol	1.40 [−0.69; 3.49]	n/a	0.38 [−2.23; 2.99]	n/a	-†	n/a	−0.06 [−0.28; 0.16]
Etanercept	-†	n/a	-†	n/a	-†	n/a	-†
Golimumab	−0.72 [−2.99; 1.54]	n/a	−0.36 [−3.40; 2.68]	n/a	-†	n/a	−0.20 [−0.43; 0.03]
Infliximab	0.64 [−2.07; 3.34]	n/a	2.27 [−1.35; 5.89]	n/a	-†	n/a	-†

Comparison (treatment in combination with MTX)	SF-36 PCS		SF-36 MCS		Fatigue VAS / NRS		Fatigue BRAF-MDQ / FACIT-Fatigue*
	MD [95% CI]	SMD [95% CI]	MD [95% CI]	SMD [95% CI]	MD [95% CI]	SMD [95% CI]	SMD [95% CI]
Effects are shown in both directions and are therefore listed twice; effects in bold font represent an added or less benefit for the first biologic; effect estimates are highlighted in grey if direct evidence was incorporated; SF-36: positive values for MD or SMD = improvement for the first biologic; VAS / NRS: negative values for MD or SMD = improvement for the first biologic; BRAF-MDQ / FACIT-Fatigue: positive values for SMD = improvement for the first biologic (effects for BRAF-MDQ were inverted during standardization). * As BRAF-MDQ and FACIT-Fatigue have different outcome measures, network meta-analysis was not performed using mean differences but standardized values only. † no study data available BRAF-MDQ = Bristol rheumatoid arthritis fatigue - multidimensional questionnaire; CI = confidence interval; FACIT-Fatigue = functional assessment of chronic illness therapy-fatigue; MCS = mental component summary score; MD = mean difference; MTX = methotrexate; n/a = not applicable; NRS = numerical rating scale; PCS = physical component summary score; SF-36: short form 36 health survey; SMD = standardized mean difference (Hedges' g); VAS = visual analogue scale							

Supplement Table 23: Network meta-analysis estimates for each comparison of biologic treatments for discontinuation due to adverse event, serious infections and mortality

Comparison (treatment in combination with MTX)	**Discontinuation due to adverse event RR [95 %-CI]**	**Serious infections RR [95 %-CI]**	**Mortality RR [95 %-CI]**
Abatacept vs.			
Adalimumab	0.67 [0.36; 1.26]	0.79 [0.38; 1.64]	0.51 [0.13; 2.11]
Anakinra	**0.12 [0.02; 0.61]**	1.05 [0.39; 2.88]	0.75 [0.15; 3.86]
Certolizumab pegol	0.42 [0.14; 1.22]	**0.22 [0.06; 0.85]**	0.80 [0.13; 5.02]
Etanercept	1.28 [0.39; 4.21]	0.94 [0.29; 3.10]	1.14 [0.06; 21.14]
Golimumab	0.55 [0.14; 2.15]	0.29 [0.04; 2.13]	0.69 [0.06; 7.95]
Infliximab	1.05 [0.35; 3.18]	3.48 [0.83; 14.62]	2.47 [0.22; 28.12]
Tocilizumab	**0.41 [0.18; 0.93]**	0.74 [0.26; 2.17]	0.84 [0.15; 4.60]
Adalimumab vs.			
Abatacept	1.49 [0.79; 2.81]	1.27 [0.61; 2.62]	1.94 [0.47; 7.94]
Anakinra	**0.18 [0.04; 0.87]**	1.33 [0.48; 3.68]	1.46 [0.25; 8.53]
Certolizumab pegol	0.62 [0.23; 1.70]	0.28 [0.07; 1.09]	1.56 [0.22; 10.95]
Etanercept	1.91 [0.62; 5.90]	1.19 [0.36; 3.96]	2.22 [0.11; 44.22]
Golimumab	0.83 [0.22; 3.04]	0.37 [0.05; 2.70]	1.34 [0.11; 16.86]
Infliximab	1.57 [0.55; 4.44]	4.40 [1.04; 18.65]*	4.79 [0.38; 59.65]
Tocilizumab	0.61 [0.29; 1.27]	0.94 [0.32; 2.78]	1.64 [0.27; 10.12]
Anakinra vs.			
Abatacept	**8.27 [1.64; 41.61]**	0.95 [0.35; 2.60]	1.33 [0.26; 6.88]
Adalimumab	**5.54 [1.15; 26.63]**	0.75 [0.27; 2.07]	0.69 [0.12; 4.03]
Certolizumab pegol	3.46 [0.60; 19.83]	**0.21 [0.05; 0.86]**	1.07 [0.14; 8.48]
Etanercept	**10.58 [1.71; 65.41]**	0.89 [0.25; 3.16]	1.53 [0.07; 32.88]
Golimumab	4.57 [0.66; 31.63]	0.28 [0.04; 2.11]	0.92 [0.07; 12.71]
Infliximab	**8.68 [1.48; 50.90]**	3.31 [0.74; 14.73]	3.29 [0.24; 44.99]
Tocilizumab	3.36 [0.67; 16.82]	0.71 [0.22; 2.23]	1.13 [0.16; 7.90]
Certolizumab pegol vs.			
Abatacept	2.39 [0.82; 6.99]	**4.52 [1.17; 17.41]**	1.25 [0.20; 7.80]
Adalimumab	1.60 [0.59; 4.37]	3.57 [0.92; 13.86]	0.64 [0.09; 4.51]
Anakinra	0.29 [0.05; 1.66]	**4.75 [1.16; 19.49]**	0.93 [0.12; 7.39]
Etanercept	3.06 [0.78; 11.96]	4.25 [0.90; 20.01]	1.43 [0.06; 34.20]
Golimumab	1.32 [0.29; 5.99]	1.32 [0.14; 12.13]	0.86 [0.05; 13.45]
Infliximab	2.51 [0.69; 9.13]	**15.72 [2.75; 89.92]**	3.07 [0.20; 47.64]
Tocilizumab	0.97 [0.33; 2.82]	3.36 [0.78; 14.45]	1.05 [0.13; 8.71]

Comparison (treatment in combination with MTX)	Discontinuation due to adverse event RR [95 %-CI]	Serious infections RR [95 %-CI]	Mortality RR [95 %-CI]
Etanercept vs.			
Abatacept	0.78 [0.24; 2.57]	1.06 [0.32; 3.50]	0.87 [0.05; 16.13]
Adalimumab	0.52 [0.17; 1.62]	0.84 [0.25; 2.79]	0.45 [0.02; 8.94]
Anakinra	**0.09 [0.02; 0.58]**	1.12 [0.32; 3.95]	0.65 [0.03; 14.09]
Certolizumab pegol	0.33 [0.08; 1.28]	0.24 [0.05; 1.11]	0.70 [0.03; 16.81]
Golimumab	0.43 [0.09; 2.13]	0.31 [0.04; 2.60]	0.60 [0.02; 21.27]
Infliximab	0.82 [0.20; 3.30]	3.70 [0.73; 18.80]	2.15 [0.06; 75.53]
Tocilizumab	0.32 [0.10; 1.04]	0.79 [0.21; 2.95]	0.74 [0.03; 16.36]
Golimumab vs.			
Abatacept	1.81 [0.47; 7.03]	3.42 [0.47; 24.80]	1.45 [0.13; 16.77]
Adalimumab	1.21 [0.33; 4.46]	2.70 [0.37; 19.70]	0.75 [0.06; 9.43]
Anakinra	0.22 [0.03; 1.52]	3.60 [0.47; 27.24]	1.09 [0.08; 15.05]
Certolizumab pegol	0.76 [0.17; 3.43]	0.76 [0.08; 6.93]	1.17 [0.07; 18.28]
Etanercept	2.32 [0.47; 11.43]	3.21 [0.38; 26.88]	1.66 [0.05; 58.80]
Infliximab	1.90 [0.41; 8.83]	**11.89 [1.23; 115.02]**	3.58 [0.15; 86.43]
Tocilizumab	0.73 [0.19; 2.84]	2.54 [0.32; 19.91]	1.23 [0.09; 17.57]
Infliximab vs.			
Abatacept	0.95 [0.31; 2.88]	0.29 [0.07; 1.21]	0.41 [0.04; 4.62]
Adalimumab	0.64 [0.23; 1.80]	0.23 [0.05; 0.96]*	0.21 [0.02; 2.60]
Anakinra	**0.12 [0.02; 0.67]**	0.30 [0.07; 1.35]	0.03 [0.02; 4.15]
Certolizumab pegol	0.40 [0.11; 1.45]	**0.06 [0.01; 0.36]**	0.33 [0.02; 5.04]
Etanercept	1.22 [0.30; 4.89]	0.27 [0.05; 1.37]	0.46 [0.01; 16.26]
Golimumab	0.53 [0.11; 2.44]	**0.08 [0.01; 0.81]**	0.28 [0.01; 6.73]
Tocilizumab	0.39 [0.13; 1.16]	**0.21 [0.05; 0.997]**	0.34 [0.02; 4.84]
Tocilizumab vs.			
Abatacept	**2.46 [1.07; 5.67]**	1.34 [0.46; 3.92]	1.19 [0.22; 6.47]
Adalimumab	1.65 [0.79; 3.47]	1.06 [0.36; 3.13]	0.61 [0.10; 3.77]
Anakinra	0.30 [0.06; 1.49]	1.41 [0.45; 4.45]	0.89 [0.13; 6.23]
Certolizumab pegol	1.03 [0.35; 2.99]	0.30 [0.07; 1.28]	0.95 [0.11; 7.88]
Etanercept	3.15 [0.96; 10.30]	1.26 [0.34; 4.70]	1.36 [0.06; 30.11]
Golimumab	1.36 [0.35; 5.26]	0.39 [0.05; 3.08]	0.82 [0.06; 11.70]
Infliximab	2.59 [0.86; 7.78]	**4.67 [1.003; 21.77]**	2.92 [0.21; 41.41]

Effects are shown in both directions and are therefore listed twice; effects in bold font represent an added or less benefit or harm for the first biologic; effects are shown in grey if a direct comparisons is included in the network meta-analysis estimate

* Data not interpreted as added or less harm (sensitivity analyses for similarity assumptions did not confirm results)

CI = confidence interval; MTX = methotrexate; RR = risk ratio

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